Antibiotics for exacerbations of chronic obstructive pulmonary disease

Vollenweider, Daniela J ; Jarrett, Harish ; Steurer-Stey, Claudia A ; Garcia-Aymerich, Judith ; Puhan, Milo A

Abstract: BACKGROUND: Many patients with an exacerbation of chronic obstructive pulmonary disease (COPD) are treated with antibiotics. However, the value of antibiotics remains uncertain as systematic reviews and clinical trials have shown conflicting results. OBJECTIVES: To assess the effects of antibiotics in the management of acute COPD exacerbations on treatment failure as observed between seven days and one month after treatment initiation (primary outcome) and on other patient-important outcomes (mortality, adverse events, length of hospital stay). SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and other electronically available databases up to September 2012. SELECTION CRITERIA: Randomised controlled trials (RCTs) in people with acute COPD exacerbations comparing antibiotic therapy and placebo with a follow-up of at least seven days. DATA COLLECTION AND ANALYSIS: Two review authors independently screened references and extracted data from trial reports. We kept the three groups of outpatients, inpatients and patients admitted to the intensive care unit (ICU) separate for benefit outcomes and mortality because we considered them to be clinically too different to be summarised in one group. We considered outpatients to have a mild to moderate exacerbation, inpatients to have a severe exacerbation and ICU patients to have a very severe exacerbation. Where outcomes or study details were not reported we requested missing data from the authors of the primary studies. We calculated pooled risk ratios (RR) for treatment failure, Peto odds ratios (OR) for rare events (mortality and adverse events) and weighted mean differences (MD) for continuous outcomes using fixed-effect models. We used GRADE to assess the quality of the evidence. MAIN RESULTS: Sixteen trials with 2068 participants were included. In outpatients (mild to moderate exacerbations), there was evidence of low quality that antibiotics did statistically significantly reduce the risk for treatment failure between seven days and one month after treatment initiation (RR 0.75; 95% CI 0.60 to 0.94; I(2) = 35%) but they did not significantly reduce the risk when the meta-analysis was restricted to currently available drugs (RR 0.80; 95% CI 0.63 to 1.01; I(2) = 33%). Evidence of high quality showed that antibiotics statistically significantly reduced the risk of treatment failure in inpatients with severe exacerbations (ICU not included) (RR 0.77; 95% CI 0.65 to 0.91; I(2) = 47%) regardless of whether restricted to current drugs. The only trial with 93 patients admitted to the ICU showed a large and statistically significant effect on treatment failure (RR 0.19; 95% CI 0.08 to 0.45; high-quality evidence).Evidence of low-quality from four trials in inpatients showed no effect of antibiotics on mortality (Peto OR 1.02; 95% CI 0.37 to 2.79). High-quality evidence from one trial showed a statistically significant effect on mortality in ICU patients (Peto OR 0.21; 95% CI 0.06 to 0.72). Length of hospital stay (in days) was similar in the antibiotics and placebo groups except for the ICU study where antibiotics statistically significantly reduced length of hospital stay (mean difference -9.60 days; 95% CI -12.84 to -6.36 days). One trial showed no effect of antibiotics on re-exacerbations between two and six weeks after treatment initiation. Only one trial (N = 35) reported health-related quality of life but did not show a statistically significant difference between the treatment and control group.Evidence of moderate quality showed that the overall incidence of adverse events was higher in the antibiotics groups (Peto OR 1.53; 95% CI 1.03 to 2.27). Patients treated with antibiotics experienced statistically significantly more diarrhoea based on three trials (Peto OR 2.62; 95% CI 1.11 to 6.17; high-quality evidence). AUTHORS' CONCLUSIONS: Antibiotics for COPD exacerbations showed large and consistent beneficial effects across outcomes of patients admitted to an ICU. However, for outpatients and

inpatients the results were inconsistent. The risk for treatment failure was significantly reduced in both inpatients and outpatients when all trials (1957 to 2012) were included but not when the analysis for outpatients was restricted to currently used antibiotics. Also, antibiotics had no statistically significant effect on mortality and length of hospital stay in inpatients and almost no data on patient-reported outcomes exist. These inconsistent effects call for research into clinical signs and biomarkers that help identify patients who benefit from antibiotics and patients who experience no effect, and in whom downsides of antibiotics (side effects, costs and multi-resistance) could be avoided.

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[Intervention Review]

Antibiotics for exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Background

Many patients with an exacerbation of chronic obstructive pulmonary disease (COPD) are treated with antibiotics. However, the value of antibiotics remains uncertain as systematic reviews and clinical trials have shown conflicting results.

Objectives

To assess the effects of antibiotics in the management of acute COPD exacerbations on treatment failure as observed between seven days and one month after treatment initiation (primary outcome) and on other patient-important outcomes (mortality, adverse events, length of hospital stay).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and other electronically available databases up to September 2012.

Selection criteria

Randomised controlled trials (RCTs) in people with acute COPD exacerbations comparing antibiotic therapy and placebo with a follow-up of at least seven days.

Data collection and analysis

Two review authors independently screened references and extracted data from trial reports. We kept the three groups of outpatients, inpatients and patients admitted to the intensive care unit (ICU) separate for benefit outcomes and mortality because we considered them to be clinically too different to be summarised in one group. We considered outpatients to have a mild to moderate exacerbation, inpatients to have a severe exacerbation and ICU patients to have a very severe exacerbation. Where outcomes or study details were not reported we requested missing data from the authors of the primary studies. We calculated pooled risk ratios (RR) for treatment failure, Peto odds ratios (OR) for rare events (mortality and adverse events) and weighted mean differences (MD) for continuous outcomes using fixed-effect models. We used GRADE to assess the quality of the evidence.

Main results

Sixteen trials with 2068 participants were included. In outpatients (mild to moderate exacerbations), there was evidence of low quality that antibiotics did statistically significantly reduce the risk for treatment failure between seven days and one month after treatment initiation (RR 0.75; 95% CI 0.60 to 0.94; I^2 = 35%) but they did not significantly reduce the risk when the meta-analysis was restricted to currently available drugs (RR 0.80; 95% CI 0.63 to 1.01; I^2 = 33%). Evidence of high quality showed that antibiotics statistically significantly reduced the risk of treatment failure in inpatients with severe exacerbations (ICU not included) (RR 0.77; 95% CI 0.65 to 0.91; I^2 = 47%) regardless of whether restricted to current drugs. The only trial with 93 patients admitted to the ICU showed a large and statistically significant effect on treatment failure (RR 0.19; 95% CI 0.08 to 0.45; high-quality evidence).

Evidence of low-quality from four trials in inpatients showed no effect of antibiotics on mortality (Peto OR 1.02; 95% CI 0.37 to 2.79). High-quality evidence from one trial showed a statistically significant effect on mortality in ICU patients (Peto OR 0.21; 95% CI 0.06 to 0.72). Length of hospital stay (in days) was similar in the antibiotics and placebo groups except for the ICU study where antibiotics statistically significantly reduced length of hospital stay (mean difference -9.60 days; 95% CI -12.84 to -6.36 days). One trial showed no effect of antibiotics on re-exacerbations between two and six weeks after treatment initiation. Only one trial (N = 35) reported health-related quality of life but did not show a statistically significant difference between the treatment and control group.

Evidence of moderate quality showed that the overall incidence of adverse events was higher in the antibiotics groups (Peto OR 1.53; 95% CI 1.03 to 2.27). Patients treated with antibiotics experienced statistically significantly more diarrhoea based on three trials (Peto OR 2.62; 95% CI 1.11 to 6.17; high-quality evidence).

Authors' conclusions

Antibiotics for COPD exacerbations showed large and consistent beneficial effects across outcomes of patients admitted to an ICU. However, for outpatients and inpatients the results were inconsistent. The risk for treatment failure was significantly reduced in both inpatients and outpatients when all trials (1957 to 2012) were included but not when the analysis for outpatients was restricted to currently used antibiotics. Also, antibiotics had no statistically significant effect on mortality and length of hospital stay in inpatients and almost no data on patient-reported outcomes exist. These inconsistent effects call for research into clinical signs and biomarkers that help identify patients who benefit from antibiotics and patients who experience no effect, and in whom downsides of antibiotics (side effects, costs and multi-resistance) could be avoided.

PLAIN LANGUAGE SUMMARY

Antibiotics for exacerbations of chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a chronic condition, often caused by smoking, which affects the passage of air in and out of the lungs. Exacerbations of COPD are defined as a sustained worsening of the patient's symptoms from their usual stable state and commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. Antibiotics are frequently prescribed for exacerbations in patients with COPD although the cause of exacerbations is often difficult to determine (viral, bacterial, environmental). We did this systematic review to find out if there is good evidence for using antibiotics for exacerbations of COPD and if benefits of taking antibiotics in individuals outweigh potential harms for individual patients and the risks of multi-resistant bacteria to the population.

We found 16 randomised studies compared antibiotics with placebo in a total of 2068 COPD patients who presented with a wide range of severities of exacerbations. Analyses showed that antibiotics reduce treatment failures (no improvement) compared with placebo in hospitalised patients with severe exacerbations. In outpatients with mild to moderate exacerbations, the evidence is more unclear because analyses showed a reduction of treatment failure when all studies and antibiotics were considered, but analyses did not suggest such an effect when they were restricted to antibiotics in current use. Length of hospital stay and mortality were not reduced by antibiotics in hospitalised patients except for those who needed treatment on the intensive care unit. Patients treated with antibiotics experienced diarrhoea twice as often as patients receiving placebo. Severity of underlying COPD could not be compared across trials because lung function and other parameters were reported inconsistently between trials.

Current evidence shows that antibiotics reduce treatment failures in patients who are hospitalised for the treatment of a COPD exacerbation, and to a lesser extent in outpatients. Mortality is only reduced by antibiotics in patients with very severe exacerbations who need treatment in the intensive care unit. The rather small and inconsistent effects of antibiotics on treatment failure suggest that antibiotics are effective in some patients but not in all inpatients and outpatients. Future high-quality studies should explore how

antibiotic therapy may be targeted towards patients who benefit by using clinical signs (e.g. purulent sputum) or biomarkers at the time when patients present to the primary care doctor or emergency department.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotics for exacerbations of chronic obstructive pulmonary disease

Patient or population: patients with exacerbations of chronic obstructive pulmonary disease
Settings: outpatient and inpatient reported together in the same table (see subgroups)
Intervention: antibiotics versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antibiotics versus placebo				
Treatment failure up to 4 weeks[1] **Subgroup: outpatient**	**275 per 1000**	**206 per 1000** (165 to 259)	**RR 0.75** (0.60 to 0.94)	931 (7 studies)	⊕⊕◯◯ **low** [2,3]	Antibiotics: - amoxicillin-clavulanic acid - trimethoprim/ sulphamethoxazole - oxytetracycline - amoxicillin - amoxicillin and co-trimoxazol
Treatment failure up to 4 weeks[1] **Subgroup: inpatient**	**520 per 1000**	**401 per 1000** (338 to 473)	**RR 0.77** (0.65 to 0.91)	612 (4 studies)	⊕⊕⊕⊕ **high** [4]	Antibiotics: - amoxicillin-clavulanic acid and trimethoprim/ sulphamethoxazole - doxycycline - tetracycline hydrochloride or chloramphenicol - penicillin and streptomycin

Treatment failure up to 4 weeks[1] **Subgoup: ICU**	**565 per 1000**	**107 per 1000** (45 to 254)	**RR 0.19** (0.08 to 0.45)	93 (1 study)	⊕⊕⊕⊕ **high**	Antibiotics: - ofloxacine
All-cause mortality **Subgroup: inpatients**	**35 per 1000**	**36 per 1000** (13 to 92)	**OR 1.02** (0.37 to 2.79)	531 (4 studies)	⊕⊕◯◯ **low** [5,6]	Antibiotics: - tetracycline hydrochloride or chloramphenicol - penicillin and streptomycin - chloramphenicol - doxycycline
All-cause mortality **Subgroup: ICU**	**217 per 1000**	**55 per 1000** (16 to 167)	**OR 0.21** (0.06 to 0.72)	93 (1 study)	⊕⊕⊕⊕ **high** [7]	Antibiotics: - ofloxacine
Adverse events - diarrhoea	**18 per 1000**	**45 per 1000** (19 to 99)	**OR 2.62** (1.11 to 6.17)	698 (3 studies)	⊕⊕⊕⊕ **high**	Antibiotics: - amoxicillin-clavulanic acid - amoxicillin - ofloxacine
Adverse events - overall (adverse events not separated)	**74 per 1000**	**109 per 1000** (76 to 154)	**OR 1.53** (1.03 to 2.27)	1243 (5 studies)	⊕⊕⊕◯ **moderate** [8]	Antibiotics: - amoxicillin-clavulanic acid - doxycycline - amoxicillin - ofloxacine

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; ICU: intensive care unit; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics.

[2] (- 1 inconsistency). Discrepancy between the statistical significance of the meta-analysis that includes all trials (RR 0.75; 95% CI 0.60 to 0.94) vs. the meta-analysis that is restricted to currently used drugs (amoxicillin-clavulanic acid, trimethoprim/ sulphamethoxazole, doxycycline, penicillin; RR 0.80; 95% CI 0.63 to 1.01).

[3] (-1 limitations). For one trial (Blasi) not all results are available.

[4] (no downgrading). The heterogeneity was caused by two small trials that contribute only 14% to the pooled estimate. Two larger trials have the most weight in the meta-analysis and show almost identical point estimates, therefore we did not downgrade for inconsistency.

[5] (-1 inconsistency). Substantial heterogeneity across trials with the largest trial showing an increase in mortality and the three small trials suggesting a decrease in mortality.

[6] (- 1 imprecision). Wide 95% CI that precludes any conclusion about the effects of antibiotics on mortality in inpatients.

[7] (no downgrading). The CI is relatively wide; however, because the upper limit of the 95% CI (0.72) as the most conservative effect estimate shows an at least moderate effect of antibiotics on mortality we did not downgrade.

[8] (- 1 imprecision). Lower limit of 95% CI is very close to 1.0 and it is uncertain if lower limit would be below 1.0 with additional trials.

BACKGROUND

The prescription of antibiotics for the treatment of exacerbations in patients with chronic obstructive pulmonary disease (COPD) has been, and continues to be, controversial. This controversy is largely based upon data suggesting that only about half of the exacerbations are of bacterial origin while other causes include viral infections or environmental irritants (Patel 2002; Seemungal 2001; Sethi 2004). One study by Bafadhel 2011 suggested that most exacerbations can be categorised as either bacteria-predominant, eosinophil-predominant, virus-predominant and pauci-inflammatory and thus may be susceptible to antibiotics or corticosteroids or, in the future, to newly developed antiviral drugs.

Antibiotics are widely prescribed (Jones 2008; Pretto 2012). Reasons for using antibiotics include the belief that the origin of an exacerbation is most likely to be a bacterial infection but also to 'be on the safe side' and prevent complications of an exacerbation such as pneumonia. Since side effects of antibiotics are mostly relatively minor, the potential benefits of antibiotics may often appear to outweigh its harms. The most important arguments against inappropriate use and overuse of antibiotics are the worldwide growing problem of multi-resistance (WHO factsheet no. 194), polypharmacy and costs. Current guidelines (GOLD 2011; NICE 2010) do not recommend antibiotics in general but recommend antibiotic therapy if all three cardinal symptoms (increased dyspnoea, sputum and cough) exist or with two of the three cardinal symptoms, if increased purulence is one of them, which may or may not be indicative of a bacterial exacerbation. However, there is currently no high-quality evidence to support this recommendation. In addition, healthcare providers may not always see that sputum and description of the patient may be unreliable.

Why it is important to do this review

There are several important reasons to conduct this systematic review. A systematic review of the literature informs patients, healthcare providers and clinical practice guideline developers in a transparent way (to minimise bias) about the effects of antibiotics on patient-important outcomes. This is important since antibiotics are likely to be perceived as beneficial in clinical practice by patients and healthcare providers because most patients recover within some weeks. However, only placebo-controlled trials can determine the cause of such recovery, which might be because of the natural recovery from exacerbations (i.e. without antibiotics), the effects of antibiotics or some other concomitant treatments such a systemic corticosteroids. Knowledge about the effects of antibiotics compared to placebo is also important to appreciate the results of the many randomised trials that compare different antibiotics. Only if antibiotics are effective at all will such head-to-head trials provide useful information (Puhan 2008).
There is growing recognition that COPD is a very heterogeneous disease (Garcia-Aymerich 2011) and exacerbations are heterogeneous events (Bafadhel 2011). This systematic review may also provide some guidance on the effects of antibiotics in different patients. Finally, systematic reviews provide useful guidance on how strong recommendations can be made for clinical practice and where more research is needed. Thus, given the uncertainties about the use of antibiotics for COPD exacerbations, this systematic review provides useful information in several respects.
This review is partly based on the protocol of a withdrawn Cochrane review on the same topic (Ram 2006) and the standard methods of the Cochrane Collaboration.

OBJECTIVES

To assess the effects of antibiotics in the management of acute COPD exacerbations on treatment failure as observed between seven days and one month after treatment initiation (primary outcome) and on other patient-important outcomes (mortality, adverse events, length of hospital stay).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) using an antibiotic in the treatment group and placebo in the control group.

Types of participants

Patients with acute exacerbations of COPD (defined as a worsening of a previous stable situation with symptoms such as increased dyspnoea, increased cough, increased sputum volume or change in sputum colour).
We considered studies eligible if more than 90% of patients had a clinical (physician-based) diagnosis of COPD or, ideally, spirometrically confirmed COPD and patients were over 40 years of age. For trials with physician-based diagnosis of COPD (also chronic bronchitis in older studies) we only considered studies when over 90% of patients had a smoking history. We accepted physician-based diagnosis of COPD because spirometry has limited value during an acute exacerbation of COPD and because restricting the systematic review to patients with spirometrically confirmed COPD would be limited to trials where patients at risk for exacerbations were enrolled in stable state and randomised when they actually suffered from an exacerbation. We excluded studies of patients with acute bronchitis, pneumonia, asthma or bronchiectasis.

Types of interventions

Oral or intravenous antibiotics administered daily for a minimum period of at least two days. All studies using antibiotics for the prevention of exacerbations were excluded as this addresses a different question. Whether or not oral corticosteroids were used additionally was not an inclusion or exclusion criterion.

Types of outcome measures

Primary outcomes

- Treatment failure as observed between seven days and one month after treatment initiation (no resolution or deterioration of symptoms after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics or other medication).

Secondary outcomes

- Treatment failure as observed between seven and 14 days after treatment initiation.
- All-cause mortality.
- Duration of hospital admission (for inpatients).
- Admission to an intensive care unit (ICU).
- Re-exacerbations within ≥ two to six weeks since beginning of index exacerbation (inpatient or outpatient treatment, rates or time to event).
- Adverse events.
- Improvement in dyspnoea.
- Hospital admission.
- Health-related quality of life or functional status measures.
- Time off work.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). All records in the Specialised Register coded as 'COPD' were searched using the following terms:

- antibiotic* or penicillin* or amoxycillin or ampicillin or cefalosporin* or cefaclor or cefalexine or cephalotin or cefazolin or cefixime or cefotaxime or cefpodoxime or cephradine or ceftizoxime or ceftriaxone or cefuroxime or tetracyclin* or demeclocycline or doxycycline or minocycline or oxytetracycline or *cycline or macrolides or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin or *thromycin or (*mycin) or fluoroquinoln* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or *floxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem.

A search of ClinicalTrials.gov was also conducted. Databases were searched from 2005 (their inception) to April 2012. The search from inception to 2006 is described elsewhere (Puhan 2007). There was no restriction on the language of publication.

Searching other resources

Bibliographies of each selected RCT, and other systematic reviews, were scrutinised for additional potential RCTs. Authors of identified RCTs and pharmaceutical companies producing antibiotics were contacted for other published, unpublished or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of all identified citations without imposing any language restrictions. The review authors then independently evaluated the full text of articles that seemed potentially eligible by one of the review authors. Any disagreements were resolved by consensus with close attention to the inclusion/exclusion criteria. All studies that did not fulfil all of the criteria were excluded and their bibliographic details listed, with the reason for exclusion.

Data extraction and management

Two review authors independently abstracted data, which was double checked and entered into Review Manager 5.1 software (RevMan 2011).

Assessment of risk of bias in included studies

We assessed the risk of bias using the domain-based approach described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). The domains included an assessment of how the random sequence was generated, allocation concealment was ensured, blinding of participants and personnel and outcome assessors was applied, and whether an intention-to-treat analysis was used. Any disagreements between review authors were resolved by discussion. In addition, we used the GRADE approach to determine the quality of evidence using the standard criteria risk of bias,

inconsistency, indirectness, imprecision and other biases (Guyatt 2011).

We generated a 'Summary of findings table' for the most important outcomes (treatment failure, all-cause mortality, overall adverse events and diarrhoea) (Summary of findings for the main comparison) and used GRADEpro software and recommendations in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011) to assess the quality of evidence.

Measures of treatment effect

We calculated pooled risk ratios (RR), Peto odds ratios (OR) for rare events and weighted mean differences (MD) for continuous outcomes.

In trials with two groups receiving different antibiotics, we treated these groups as one group if the effects of the two antibiotics did not differ in a statistically significant or clinically important way.

Dealing with missing data

When necessary we contacted study authors in order to obtain further information about their trials.

Assessment of heterogeneity

We kept the three groups of outpatients, inpatients and patients admitted to the ICU separate for most analyses except for adverse events because we considered them to be clinically too different to be summarised in one group. We considered outpatients to have a mild to moderate exacerbation, inpatients to have a severe exacerbation and ICU patients to have a very severe exacerbation (event-based definitions of severity of exacerbations). Within the analysis of outpatients and inpatients we used the heterogeneity Chi^2 statistic to assess statistical heterogeneity and expressed it by the I^2 statistic.

Assessment of reporting biases

For trials published after 1990 we tried to find the trial registration information and assessed whether all outcomes specified there were reported.

Data synthesis

We used fixed-effect models (or random-effects model if statistical heterogeneity with $I^2 > 50\%$ was observed) to calculate mean differences for continuous outcomes or inverse-variance weighted pooled RRs. For rare events and trials with similar size of treatment groups we used Peto's method to pool ORs. We also calculated number needed to treat for an additional beneficial outcome (NNTB) and 95% confidence interval (CI) and number needed to treat for an additional harmful outcome (NNTH). These were calculated using the following formula: NNT = 1/ [CER * (1 - RR)] (where CER = control event rate).

Subgroup analysis and investigation of heterogeneity

As explained above, we kept as a marker of the severity of exacerbation outpatients, inpatients and patients admitted to the ICU separate for all benefit outcomes.

Sensitivity analysis

In a sensitivity analysis we restricted the analyses to trials that evaluated at least one antibiotic that is still in current use (amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, penicillin).

RESULTS

Description of studies

Results of the search

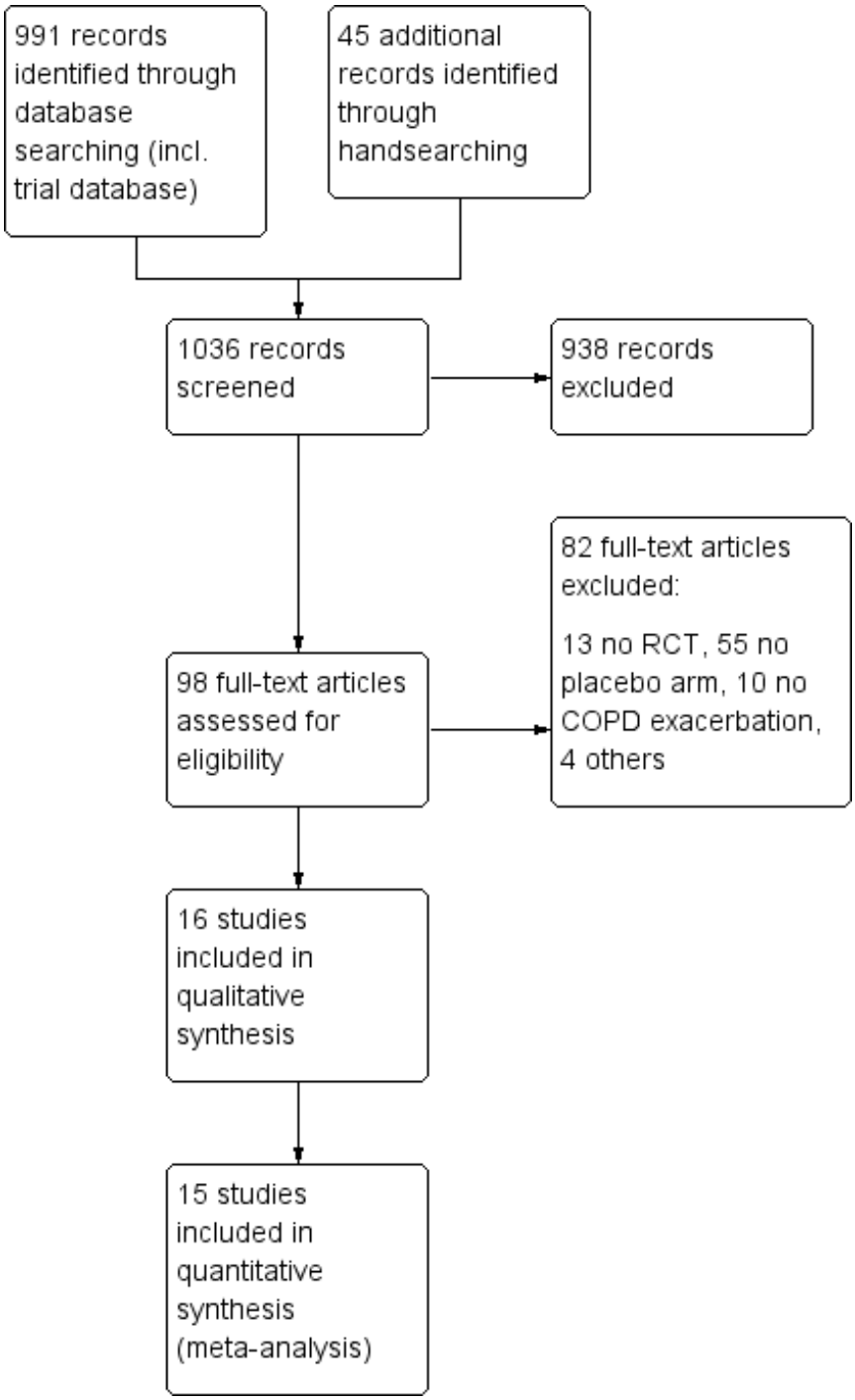
Searches to 2006

The electronic search of the former non-Cochrane review conducted by this author team (Puhan 2007) yielded 765 references. After assessing references on the basis of title and abstract, two review authors independently scanned the full text of 35 studies of the electronic search and additional 30 studies that were identified through handsearching. Four studies were ongoing trials (ABC 2009; Fartoukh 2004; NCT00170222; NCT00255983). Thirteen studies were included (Allegra 1991; Alonso Martinez 1992; Anthonisen 1987; Berry 1960; Elmes 1957; Fear 1962; Jørgensen 1992; Manresa 1987; Nouira 2001; Petersen 1967; Pines 1968; Pines 1972; Sachs 1995).

Searches from 2005 to 2012

We identified 226 citations from the update search (2005 to 2012) of electronic databases. We retrieved 25 full texts and handsearched nine protocols on www.clinicaltrials.gov. Out of this search we identified two eligible trials (Daniels 2010; Llor 2012) and through handsearching we identified one additional trial (ABC 2009) (see Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 16 studies on 2068 participants. Out of the 16 included studies, nine trials included outpatients (ABC 2009; Allegra 1991; Anthonisen 1987; Berry 1960; Elmes 1957; Fear 1962; Jørgensen 1992; Llor 2012; Sachs 1995), six trials included patients admitted to a hospital (Alonso Martinez 1992; Daniels 2010; Manresa 1987; Petersen 1967; Pines 1968; Pines 1972) and one trial included patients admitted to a medical ICU (Nouira 2001). The studies were, on average, of small sample size with a range from 19 to 310 included patients. Severity of underlying COPD could not be compared across trials because lung function and other parameters were reported inconsistently between trials. Twelve trials were reported as full reports in English language journals, one trial was published in Spanish (Alonso Martinez 1992), one in Italian (Allegra 1991), one trial was reported as a conference proceeding and medical thesis (ABC 2009) and one trial was reported as a clinical letter to a major journal (Manresa 1987). One trial (Allegra 1991) only entered the analyses on adverse effects because it reported only on treatment failure within five days of treatment initiation. We made attempts to retrieve the data on treatment failure within two weeks, which was assessed but not reported (personal communication with Dr Blasi, March 2006) but the data were not made available to us. Further details on included studies are shown in the table Characteristics of included studies and a summary of the interventions across studies can be found in Table 1.

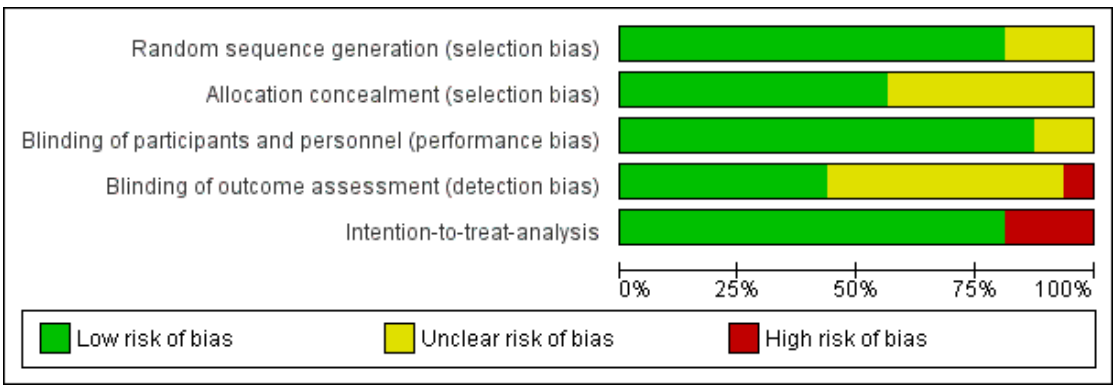
Excluded studies

We excluded most trials because they compared different types of antibiotics to each other and had no placebo arm (see Characteristics of excluded studies; Figure 1). One study was identified as an ongoing study (NCT01091493) that had just started.

Risk of bias in included studies

Overall there was relatively little risk of bias (see Figure 2). Random sequence generation, blinding of participants and personnel, and intention-to-treat analysis was correctly performed and reported by 80% of the studies. Allocation concealment and blinding of outcome assessment was correctly performed and reported by 56% of the studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

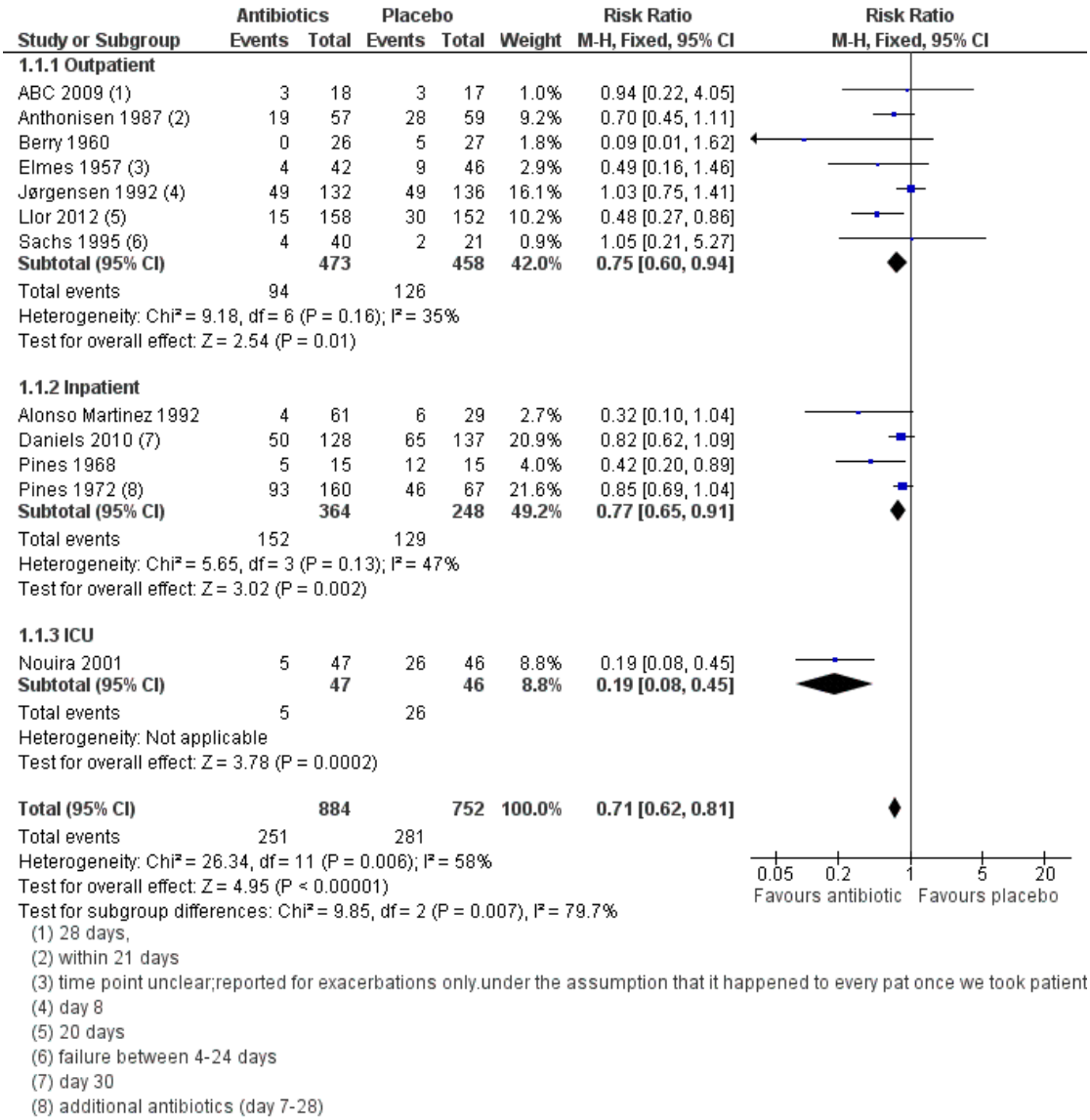
See: **Summary of findings for the main comparison** Antibiotics for exacerbations of chronic obstructive pulmonary disease

Primary outcome: treatment failure between seven days and one month of treatment initiation

Eleven studies with 1326 patients reported on this outcome (Figure 3). The follow-up period for these studies to assess treatment failure ranged from eight to 28 days. In some studies treatment failure outcome was patient reported (ABC 2009; Anthonisen 1987; Berry 1960; Daniels 2010; Elmes 1957; Jørgensen 1992; Sachs 1995), while in two trials it was provider

reported (Llor 2012; Pines 1968), defined by an additional course of antibiotics (Alonso Martinez 1992; Pines 1972) or a combined end point of additional antibiotics and death (Nouira 2001). As pre-defined we analysed treatment separately for outpatients, in-patients and patients admitted to the ICU.

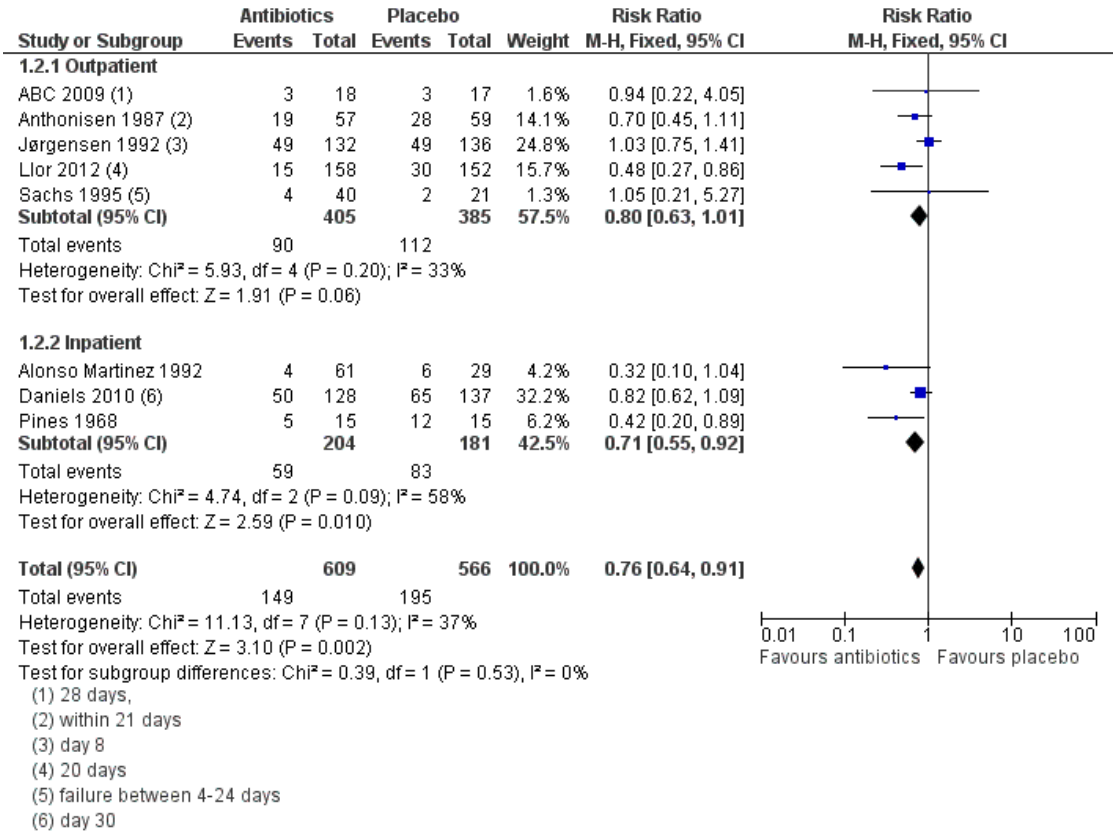
Figure 3. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics).



In outpatients (seven trials; 931 participants; Figure 3) antibiotics statistically significantly reduced the risk for treatment failure (RR 0.75; 95% CI 0.60 to 0.94; I^2 = 35%) with an NNTB of 13 (95% CI 8 to 46). Antibiotics had a statistically significant effect in inpatients (four trials; 612 participants) (RR 0.77; 95% CI 0.65 to 0.91; I^2 = 47%) with an NNTB of 10 (95% CI 6 to 45). In the ICU trial with 93 participants antibiotics showed a statistically significant effect (RR 0.19; 95% CI 0.08 to 0.45) with an NNTB of 2 (95% CI 2 to 3).

Restricting the analysis to currently used drugs (amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, penicillin) gave a different effect compared to the unrestricted analyses for outpatients (RR 0.80; 95% CI 0.63 to 1.01; Figure 4) with a non-statistically significant effect. In inpatients, the results were similar (RR 0.71; 95% CI 0.55 to 0.92).

Figure 4. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.2 Treatment failure within 4 weeks - current drugs only.



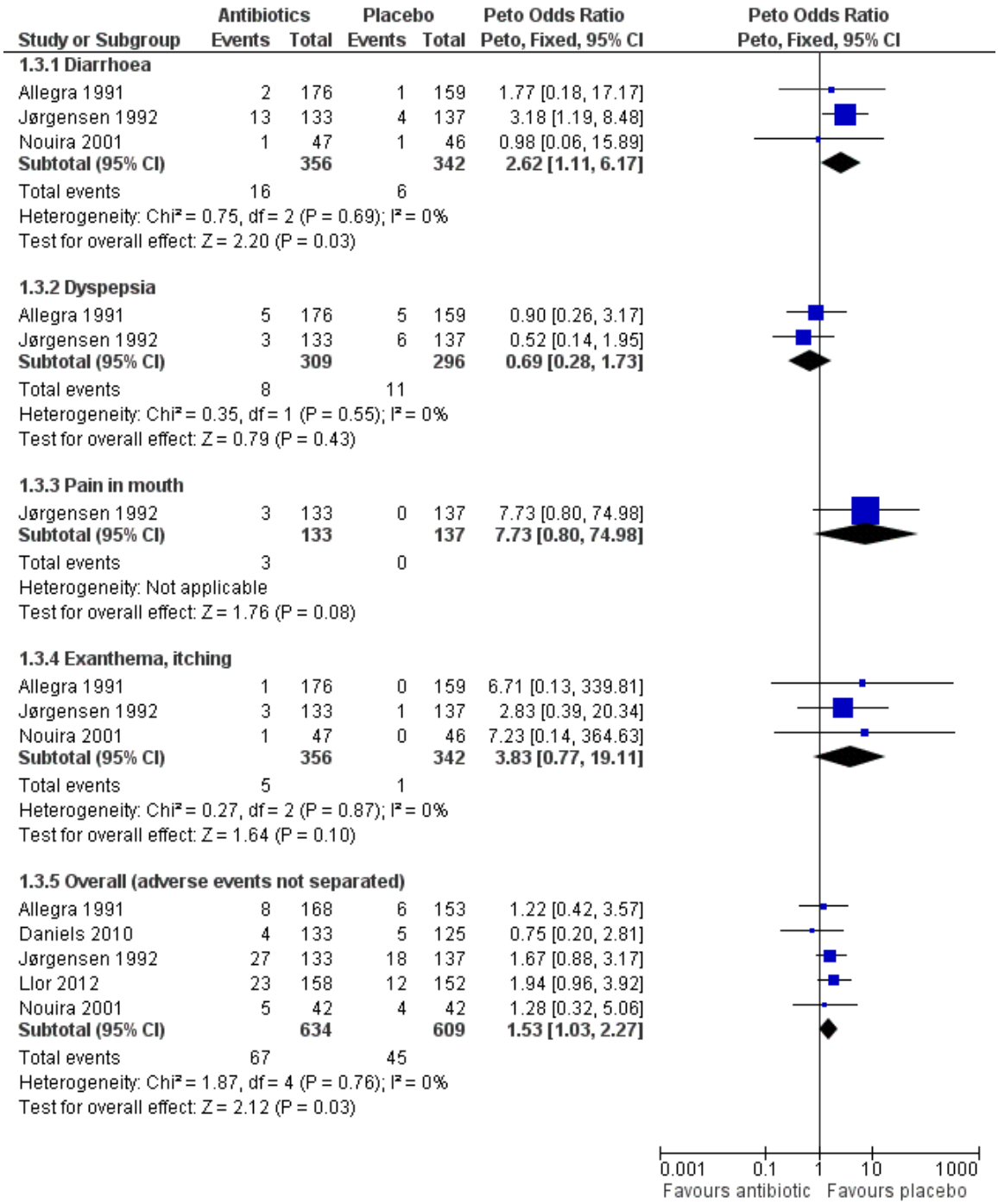
Adverse events

The pooled analysis includes only trials that evaluated currently used antibiotics.

Diarrhoea

Three studies with 398 patients (Allegra 1991; Jørgensen 1992; Nouira 2001) provided data on the number of patients experiencing diarrhoea. Figure 5 shows that patients treated with placebo had a statistically significantly lower chance of diarrhoea compared to patients treated with antibiotics (Peto OR 2.62; 95% CI 1.11 to 6.17; NNTH of 36; 95% CI 19 to 565).

Figure 5. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.3 Adverse events.



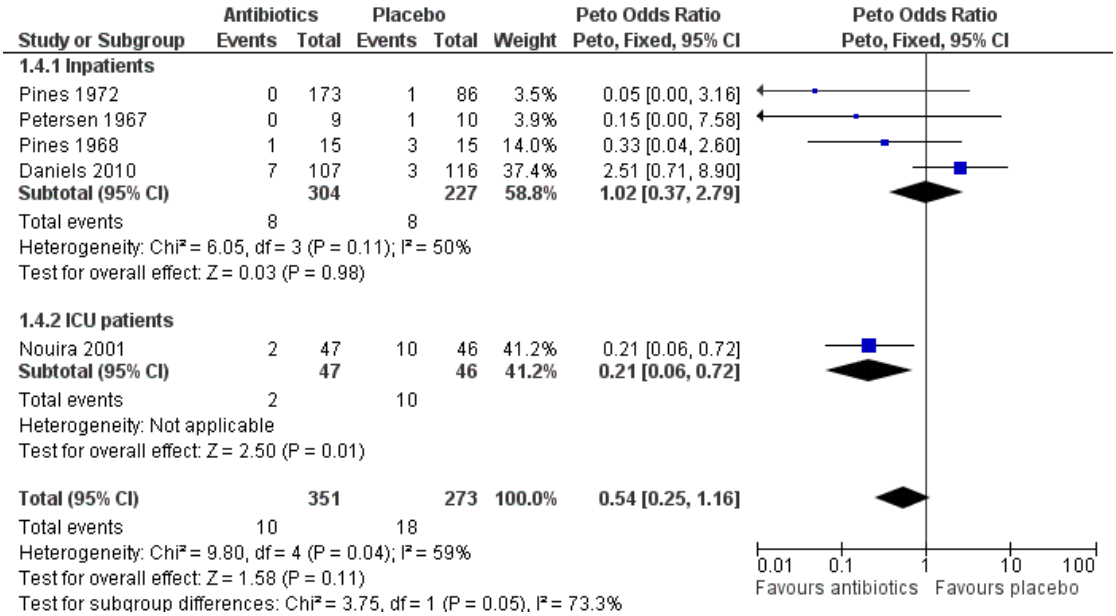
Overall adverse events

Five studies with 1243 patients (Allegra 1991; Daniels 2010; Jørgensen 1992; Llor 2012; Nouira 2001) provided data on the overall incidence of adverse events in the study groups. There were statistically significantly fewer adverse events with placebo (Peto OR 1.53; 95% CI 1.03 to 2.27; NNTH 32; 95% CI 16 to 10490). Other adverse events are shown in Figure 5.

All-cause mortality

Five trials on 624 patients, four inpatient trials (Daniels 2010; Petersen 1967; Pines 1968; Pines 1972) and one ICU trial (Nouira 2001), reported mortality. There was no statistically significant effect of antibiotics on mortality for inpatients (Peto OR 1.02; 95% CI 0.37 to 2.79) but there was a statistically significant effect in ICU patients (Peto OR 0.21; 95% CI 0.06 to 0.72; NNTB 6 (96% CI 3 to 24) (Figure 6).

Figure 6. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.4 All-cause mortality.



Duration of hospital stay

Three trials with 202 patients reported length of hospital stay (measured in days). Of these three trials two favoured neither antibiotics nor placebo (Alonso Martinez 1992; Manresa 1987). The third trial (Nouira 2001), an ICU trial, clearly favoured antibiotics (MD -9.60; 95% CI -12.84 to -6.36).

Dyspnoea

Two studies with 300 patients reported dyspnoea at the end of the study period (ABC 2009; Daniels 2010). There was no significant improvement in dyspnoea in either trial (outpatients: MD 0.00; 95% CI -0.97 to 0.97; inpatients: MD -0.60; 95% CI -1.27 to 0.07) (Analysis 1.6).

Outcomes with only one included trial

Health-related quality of life

One outpatient trial (ABC 2009) with 35 patients reported health-related quality of life and showed no statistically significant difference between the treatment and control group (MD 0.00; 95% CI -1.79 to 1.79) (Analysis 1.7).

Re-exacerbations

One trial (ABC 2009) with 35 patients reported number of patients with re-exacerbations within two to six weeks. In the antibiotics group, there were two re-exacerbations compared to one in the placebo group (RR 1.89; 95% CI 0.19 to 18.97) (Analysis 1.8).

Days off work

Elmes 1957, the oldest trial, reported days off work. The antibiotics group had statistically significantly fewer days off work compared with the placebo group (MD -5.18; 95% CI -6.08 to -4.28) (Analysis 1.9).

Grading

The 'Summary of findings' table shows that the quality of evidence was low for the effect estimates of antibiotics on treatment failure in outpatients because of the discrepancy between the statistical significance of meta-analysis that includes all trials versus the meta-analysis that is restricted to currently used drugs (amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, penicillin) and because the results from one trial were not made available by the study authors. For inpatients and patients admitted to the ICU we considered the results for the outcome treatment failure to be high. Since there was substantial heterogeneity across trials in inpatients that assessed the effects of antibiotics on mortality and because the results were imprecise we downgraded the quality of evidence to low. The quality of evidence on the effects of antibiotics on mortality in patients admitted to the ICU was high. For adverse events, we considered the quality of evidence to be high for the outcome of diarrhoea but downgraded the quality of evidence for any adverse events because of imprecision. It is uncertain if the lower limit of the 95% CI would be below 1.0 with additional trials.

DISCUSSION

Summary of main results

The meta-analyses showed that antibiotics for acute exacerbations of COPD reduced treatment failure statistically significantly for outpatients when all trials from 1957 to 2012 were included but not when the analyses were restricted to currently used antibiotics. Antibiotics had a statistically significant effect on treatment failure in inpatients and patients treated in the ICU. There was a statistically significant reduction in the risk of mortality among ICU patients with the use of antibiotics but not for inpatients (no data for outpatients available). There was a statistically significant increase in the risk of adverse events with antibiotic use compared to placebo. Length of hospital stay was not significantly reduced by antibiotics except for ICU patients. There were few data on the effects of antibiotics on health-related quality of life or other patient-reported symptoms.

Overall completeness and applicability of evidence

The severity of underlying COPD could not be studied as a potential source of heterogeneity. Trials with information on COPD severity are rare as lung function tests are difficult to perform during exacerbations and as lung function results are rarely available from the pre-exacerbation period. Also, the definitions and classifications of COPD have changed over the years so that no uniform classifications of COPD could be extracted from the studies. Nevertheless, the results from this review appear to be applicable to patients with moderate to severe COPD who typically suffer from exacerbations.

There was no common definition for severity of exacerbation that was used in the trials. There is uncertainty on the thresholds of admitting patients to hospital and whether this was comparable among trials. Thus stratification according to setting is just a proxy for the severity of exacerbation although such an event-based definition is commonly used in COPD research (Rodriguez-Roisin 2000). Our finding that the effects of antibiotics depend on the severity of exacerbations is supported by the Anthonisen 1987 trial, which showed a benefit for the most severe exacerbations but not for mild exacerbations. In contrast, the results of the meta-analyses for treatment failure in outpatients and inpatients (non-ICU patients) showed almost identical results. This may suggest that our conservative approach of keeping outpatients and inpatients separate was not necessary and that there are other determinants of hospital admission than the severity of an exacerbation only.

Only two small trials reported patient-important outcomes such as health-related quality of life or days off work, which is heavily influenced by exacerbations and one of the main targets of COPD treatments.

With a relatively high NNTH it could be argued that treating outpatients with antibiotics is not problematic as some may still benefit. This disregards the consistent and growing problem of resistance against antibiotics and the need to decrease the over-utilisation of unnecessary antibiotics (WHO factsheet no. 194).

Overall, there is a strong beneficial effect of antibiotics in ICU patients. In inpatients and outpatients there is some effect of antibiotics but the effects are small and inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay).

Quality of the evidence

We restricted our systematic review to RCTs and found 16 placebo-controlled RCTs with 2068 patients. Starting with the assumption that RCTs provide high-quality evidence, we did not downgrade the quality of evidence for risk of bias for any outcome because the risk of bias was low for most trials. We downgraded the analyses for some outcomes for inconsistency, which is not unexpected given the heterogeneity of patients with COPD. As a consequence of the small number of patients and events, we downgraded the quality of evidence for mortality in inpatients. We expect, based on our assessment of the quality of evidence, that additional trials could change the results for treatment failure in outpatients and for mortality in inpatients.

Potential biases in the review process

Although treatment failure is commonly used in meta-analyses, it is a limitation that definitions of treatment failure differ across trials. It is difficult to standardise the definition of treatment failure because it may include patient-reported symptoms, clinical signs and results from laboratory tests or imaging. However, we do not have reason to believe that different definitions of treatment failure caused heterogeneity in our meta-analyses. Also, we could not assess the influence of other factors such as season, co-morbidities or concurrent medication use such as systemic corticosteroids or bronchodilators as they were reported inconsistently and to a limited extent.

A limitation of the present systematic review is publication bias, which is a potential threat to any systematic review. Studies demonstrating a positive effect for antibiotics may be more likely to be published than negative studies. In order to minimise missing studies we used extensive trial search criteria with no language restrictions and made every effort to detect any unpublished or ongoing studies and contacted authors of the included trials, some of whom provided additional information about their data. However, we have reasons to believe that the results of two trials are not yet in the public domain and we, therefore, downgraded the quality of evidence for the outcome of treatment failure in outpatients.

Agreements and disagreements with other studies or reviews

Our systematic review is in agreement with a former review (Puhan 2007), and the findings did not change substantially with the addition of three new trials (ABC 2009; Daniels 2010; Llor 2012). We agree with the former Cochrane review on this topic (Ram 2006) on treatment failure in inpatients but we disagree with several other outcomes and the review's conclusions. The former Cochrane review used several different outcomes such as peak flow, lung function, sputum purulence and blood gases, which we believe are not the important, patient-relevant outcomes to estimate the value of antibiotics for the management of acute COPD exacerbations. Also, the former review included a study that was not an RCT (Elmes 1965) and excluded a study that actually was an RCT (Berry 1960). In addition, we were able to obtain COPD-specific data from one RCT (Sachs 1995) that reported on the results for both asthma and COPD patients. Also, our results for mortality in inpatients differ from those of the former Cochrane review because that review included the Elmes trials (Elmes 1965) and did not keep ICU and inpatients separate.

The systematic review of Saint 1995 combined results from different outcomes in a meta-analysis. Nevertheless, the authors concluded an overall combined standardised mean effect size estimate of 0.22 (95% CI 0.1 to 0.34) indicating a small but statistically significant effect favouring antibiotics over placebo. We think that combining different outcomes and using standardised effect sizes is an inappropriate way to pool results.

AUTHORS' CONCLUSIONS

Implications for practice

There is continued uncertainty as to whether antibiotics provide a benefit to COPD patients with acute exacerbations that can be treated on an outpatient basis. Current data suggest that antibiotics do not significantly reduce treatment failure or improve the patients' health-related quality of life with currently available antibiotics. In patients who need hospital admission for severe exacerbations, antibiotics do reduce treatment failures but not the length of hospital stay or mortality. Finally, antibiotics reduce mortality, treatment failures and length of hospital stay in patients who need ICU care. The results of this systematic review provide evidence for developers of guidelines to consider the evidence base but also additional factors such as patient preferences, resistance of bacteria to antibiotics and cost to make practice recommendations.

Implications for research

In the large majority of COPD patients who are treated on an outpatient basis because of mild to moderate exacerbations additional placebo-controlled trials could determine the effectiveness of antibiotics on short- and long-term outcomes and on patient-important outcomes such as health-related quality of life. It is challenging to recruit outpatients for placebo-controlled trials because of widespread beliefs about the positive effects of antibiotics. But as our review suggests, withholding antibiotics in outpatients and even in inpatients did not or only slightly increase the risk for treatment failure and mortality so that placebo-controlled RCTs are still justifiable.

The conflicting evidence raised discussions about (bio-) markers, which could predict a bacterial infection and help to select patients who benefit from antibiotic treatment and save antibiotics in those who are unlikely to benefit. Sputum purulence is one of the most

discussed indicators that could be used to guide antibiotic therapy. It is noteworthy that there are no adequately powered RCTs that assessed effect modification by the presence or absence of purulent sputum. Indirect evidence on effect modification is available from the trials included in this systematic review. Four trials (ABC 2009; Elmes 1957; Pines 1968; Pines 1972) included patients with purulent sputum only or positive gram stain, although few details on how purulent sputum was defined and measured were available. Of these four trials only one showed a statistically significant effect on treatment failure (Pines 1968) and the only most recent trial (ABC 2009) did showed no effects on any of the outcomes. Also, there is no indication from the trials included in this review that these trials show results that are different from those trials that did not restrict the study population to patients with purulent sputum. Biomarkers may also be promising to guide antibiotic treatment for COPD exacerbations. C-reactive protein (CRP) or B-type natriuretic peptide may be promising because they are relatively cheap and easily available in inpatient and outpatient settings (Llor 2012; Daniels 2010b). There are additional candidates for guiding antibiotic treatment, such as procalcitonin, but their cost currently limits their use to highly specialised settings.

There are different types of studies that could be done to determine the potential of clinical signs and biomarkers to guide antibiotic therapy for COPD exacerbations. Additional placebo-controlled trials could assess whether the effects of antibiotics (versus placebo) are different in patients with (or without) purulent sputum or with different levels of a biomarker. Such trials would require relatively large sample sizes in order to assess subgroup effects (effect modification) formally. Alternatively, more pragmatic trials could be done where physicians are randomised to using or not using a clinical sign or biomarker to guide the prescription of antibiotics. Such trials would typically be non-inferiority trials that aim to show that the clinical benefit is not worse when using a clinical sign or biomarker but that adverse effects, cost and bacterial resistance could be limited by less use of antibiotics. One Cochrane review showed that procalcitonin guidance was not associated with increased mortality or treatment failure in patients with acute respiratory infections but significantly reduced overall antibiotics use (Schuetz 2012). Finally, observational studies may be used to look into the potential of clinical signs or biomarkers to predict outcomes of patients with COPD exacerbations. Such studies could either assess the independent predictive properties of clinical signs or biomarkers, or compare the outcomes with antibiotic treatment versus no antibiotic treatment in patients with or without a clinical sign or certain biomarker levels while adequately adjusting for selection mechanisms and confounding. Such observational studies appear more feasible than additional placebo-controlled RCTs but they may often be only hypothesis generating rather than providing high-quality evidence as a basis for treatment recommendations.

Finally, it would also be important to have more high-quality evidence on the long-term effects (re-exacerbations, health-related quality of life and mortality) of antibiotics in COPD patients with mild to moderate exacerbations. Also, head-to-head antibiotic trials continue to be important in COPD patients treated for exacerbations in inpatient and ICU settings because the susceptibility of strains is dynamic and may differ over time and from setting to setting.

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[Лечење ефекти сарадње

амокицлав (амокицлав 2к) у акутној погоршања тешке хроничне опструктивне болести плућа: клиничка евалуација]. *Medicinski Pregled* 2011;**64**(3-4):178–82.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ABC 2009

Methods	RCT
Participants	Participants: outpatients seen by chest physicians received antibiotic or placebo for moderately severe exacerbations Inclusion criteria: clinical diagnosis of COPD (GOLD criteria), current or ex-smoker, aged 40 to 80 years, presenting as an outpatient with signs and symptoms of an exacerbation (change in dyspnoea, sputum volume and colour, and cough), able to produce sputum sample, 1 or 2 of: positive sputum Gram's stain, clinically relevant decrease in lung function or $\geq$ 2 exacerbations in the previous year Exclusion criteria: pneumonia, exacerbation or use of antibiotics or prednisolone 4 weeks prior to enrolment (except $\leq$ 5 mg prednisolone), other disease influencing lung function, maintenance antibiotics, hypersensitivity to amoxicillin-clavulanic acid, serious medical or psychiatric co-morbidity, uncontrolled diabetes mellitus, home oxygen therapy Baseline demographics: 35 patients included; mean age 67 years; 60% male; mean FEV_1/FVC 40% Spirometrically confirmed COPD: yes Severity of exacerbation: moderate
Interventions	Follow-up: 28 days for primary outcome and 4 months for new exacerbations Treatment group: amoxicillin-clavulanic acid 1.5 g/day for 7 days and oral prednisolone 30 mg for 7 days Control group: placebo for 7 days and oral prednisolone 30 mg for 7 days
Outcomes	Resolution of exacerbation (patient reported symptom diary) Relapses of exacerbations within 28 days Chronic respiratory questionnaire Clinical COPD questionnaire
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"

ABC 2009 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of yes or no
Intention-to-treat-analysis	Low risk	All patients were analysed in the groups to which they were randomised

Allegra 1991

Methods	RCT
Participants	Participants: patients recruited from pulmonary departments received antibiotic or placebo on an outpatient basis in case of self-reported worsening of respiratory symptoms Inclusion criteria: aged > 40 years, chronic bronchitis (defined as continuous cough and expectoration, present for at least 3 months of the year, in more than 2 consecutive years) , FEV_1 < 80% predicted Exclusion criteria: reversible obstruction, cancer, liver insufficiency, renal insufficiency, heart failure, pneumonia Baseline demographics: 335 patients included; mean age 63 years; 73% male; mean FEV_1 1.37 L/s Spirometrically confirmed COPD: yes Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 5 days Treatment group: amoxicillin-clavulanic acid 2 g/day (oral) for 5 days Control group: placebo for 5 days
Outcomes	Treatment success/failure (patient-reported symptoms and clinical signs) at 5 days (not analysed in this systematic review) Dyspnoea (not analysed in this systematic review because data were not in format that we could use) Adverse events
Notes	According to an author of the study (personal communication with Dr. Blasi, March 2006) data after 14 days of follow-up were available but not published and not made available for this review

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Allegra 1991 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Intention-to-treat-analysis	High risk	Only patients with complete follow-up were analysed

Alonso Martinez 1992

Methods	Randomised double-blinded placebo-controlled trial
Participants	Participants: patients admitted to hospital with exacerbation (increasing symptoms such as dyspnoea, sputum volume or cough) of COPD Inclusion criteria: clinical diagnosis of COPD at the time of hospital admission Exclusion criteria: antibiotic treatment during the previous 2 weeks, left ventricular failure, stroke, pneumonia, pneumothorax, non-cutaneous cancer, coma, temperature > 38 °C, psychological disorders related to COPD Baseline demographics: 90 patients included; mean age 68 years, 84% male, mean FEV_1 % predicted (SD) 29.98% (11.07) Spirometrically confirmed COPD: yes Severity of exacerbation: severe
Interventions	Mean follow-up: 7.2 days Treatment group: trimethoprim-sulphamethoxazole 1.9 g/day or amoxicillin/clavulanic acid 1.9 g/day orally for 8 days Control group: placebo for 8 days
Outcomes	Length of hospital stay Treatment success (use of additional antibiotics) Re-exacerbations (in 3 months - not analysed in this systematic review)
Notes	All patients were treated with theophylline, inhaled bronchodilators and oxygen. If the numerical score was high or FEV_1 < 40% they received, 6-methylprednisolone 0.75 mg/kg/day

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Arithmetic combination
Allocation concealment (selection bias)	Low risk	Through hospital pharmacy

Alonso Martinez 1992 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information provided
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Anthonisen 1987

Methods	Randomised double-blinded placebo-controlled trial
Participants	Participants: 173 patients were recruited from the community with stable COPD. 116 developed exacerbations (increased dyspnoea, sputum volume or sputum purulence) and each time was randomly assigned to receive antibiotics or placebo Inclusion criteria: aged > 35 years; clinical diagnosis of COPD, not asthma; FEV_1 and FVC < 70% predicted, TLC > 80% Exclusion criteria: if FEV_1 increased to 80% of predicted post bronchodilator use; other disease serious enough to influence their quality of life or clinical course (e.g. cancer, left ventricular failure, stroke) or other disease likely to require antibiotics (e.g. recurrent sinusitis or UTI) Baseline demographics: 116 patients included; mean age 67 years, 80% male, mean FEV_1 % predicted (SD): 33.9% (13.7) Spirometrically confirmed COPD: yes Severity of exacerbation: mild to moderate
Interventions	Follow-up: 21 days Treatment group: trimethoprim/sulphamethoxazole 1.9 g/day or amoxicillin 1 g/day or doxycycline 0.1 to 0.2 g/day orally for 10 days Control group: placebo for 10 days
Outcomes	Treatment failure (patient-reported symptoms) Side effects (% of exacerbations with side effects)
Notes	The analysis was based on number of patients with first exacerbations (only first exacerbation). Side effects were not analysed as they were expresses as % of all exacerbations

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random schedule
Allocation concealment (selection bias)	Unclear risk	Not reported

Anthonisen 1987 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither patients nor medical staff knew which medication was active"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medical staff"
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Berry 1960

Methods	RCT
Participants	Participants: patients at general practitioner visit for new or aggravated respiratory symptoms Inclusion criteria: chronic bronchitis (persistent or recurrent cough with diffuse physical signs in the chest, in which X-ray had excluded other disease) with exacerbation (worsening characterised by 1 or more of the following: increased cough, increased volume of sputum, increased purulence of sputum, increased breathlessness or fever) Exclusion criteria: none Baseline demographics: 58 patients included; mean age 59 years, 53% male, FEV_1 not reported Spirometrically confirmed COPD: no Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 14 days Treatment group: oxytetracycline 1 g/day (oral) for 5 days Control group: placebo for 5 days
Outcomes	Treatment success/failure (patient reported)
Notes	Patients with severe exacerbations were not included because antibiotics were deemed indispensable

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Identical bottles, key to numbers was kept by another person
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical bottles and capsules

Berry 1960 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Practitioners were blinded
Intention-to-treat-analysis	High risk	Patients with possible toxic effects from drugs were excluded

Daniels 2010

Methods	RCT
Participants	Participants: hospitalised patients with acute exacerbations of COPD Inclusion criteria: aged > 45 years, diagnosis of COPD (GOLD criteria), acute exacerbation (Anthonisen 1 and 2) Exclusion criteria: inability to take oral medication, fever (> 38.5 °C), antibiotic treatment for > 24 hours, extensive treatment with corticosteroids (> 30 mg > 4 days), history of severe exacerbation requiring mechanical ventilation, lung malignancy, other infectious disease requiring antibiotic therapy, heart failure (NYHA III-IV), apparent immunodeficiency, impaired renal function (creatinine clearance < 20 mL/min) Baseline demographics: 223 patients included; 265 exacerbations; mean age 72 years; 59.6% male; mean FEV_1 (SD) doxycycline group 43.9% (17.2%), placebo group 46.9% (18.5%) Spirometrically confirmed COPD: yes Severity of exacerbation: moderate to severe
Interventions	Mean follow-up: 30 days Treatment group: 7-day course of oral doxycycline, IV prednisolone taper Control group: 7-day course of placebo, IV prednisolone taper
Outcomes	Primary outcome: clinical response on day 30 (success/failure) Secondary outcome: clinical success day 10, dyspnoea score, adverse events, mortality
Notes	Analysis based on the number of exacerbations and patients (mortality)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	"Allocation sequence was kept in a safe at the hospital pharmacy"; "study medication was delivered in pre-numbered containers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"

Daniels 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described (only "double-blind")
Intention-to-treat-analysis	Low risk	Analysed as intention to treat and per-protocol (we used only intention to treat)

Elmes 1957

Methods	RCT
Participants	Participants: patients were instructed to take antibiotic or placebo without a doctor visit as soon as new or aggravated respiratory symptoms were present Inclusion criteria: aged < 65 years, regular employment, productive winter cough for > 3 years, during which time they had at least 2 illnesses with purulent sputum, causing loss of time from work Exclusion criteria: other disabling disease Baseline demographics: 88 patients included; mean 54 age years; 84% male; FEV_1 not stated Spirometrically confirmed COPD: no Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 17 days Treatment group: oxytetracycline 1 g/day orally for 5 to 7 days Control group: placebo for 5 to 7 days
Outcomes	Treatment success/failure (need for further antibiotics) Time off work Side effects
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Fisher and Yate's table of random numbers
Allocation concealment (selection bias)	Low risk	"Key list was held by the hospitals pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Dummy tablets... neither doctors nor patients knowing which was which"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Dummy tablets... neither doctors nor patients knowing which was which"

Elmes 1957 (*Continued*)

Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Fear 1962

Methods	RCT
Participants	Participants: patients recruited from bronchitis and asthma clinics received antibiotic or placebo as an outpatient based on case of self-reported worsening of respiratory symptoms Inclusion criteria: aged 20 to 65 years, winter cough and sputum for at least 3 years, with shortness of breath on effort without evidence of other cause; some degree of disability from the bronchitis (e.g. limitation of normal activity, loss of time at work) Exclusion criteria: none Baseline demographics: 62 patients included; mean age, % male and FEV_1 not stated Spirometrically confirmed COPD: no Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 14 days Treatment group: oxytetracycline 1 g/day (oral) for 7 days Control group: placebo for 7 days
Outcomes	Improvement of symptoms (not analysed in this systematic review) Days of illness (not analysed in this systematic review)
Notes	Second trial of the article

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	List of random numbers
Allocation concealment (selection bias)	Low risk	"Similar to that used by Elmes 1957" "identical appearance"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind" "identical appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Jørgensen 1992

Methods	Randomised double-blind placebo-controlled trial
Participants	Participants: patients with general practitioner visits for new or aggravated symptoms Inclusion criteria: aged > 18 years with acute exacerbation (subjective worsening owing to change in sputum (increased volume, change of viscosity or colour) possibly accompanied by cough or dyspnoea, lasting for more than 3 days or chronic bronchitis (defined as continuous cough and expectoration, present for at least 3 months of the year, in more than 2 consecutive years) Exclusion criteria: pneumonia (on auscultation or X-ray), temperature > 38.5 °C, heart rate > 100 beats/min, antibiotics within the previous 7 days, pregnancy, allergy to penicillin, uncompensated heart disease, treatment with oral corticosteroids or immunosuppressants Baseline demographics: 270 patients included; mean age 60 years, 43% male. FEV_1 not stated Spirometrically confirmed COPD: no Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 8 days Treatment group: amoxicillin 1.5 g (oral) for 7 days Control group: placebo for 7 days
Outcomes	Treatment failure (patient-reported symptoms) Adverse events
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to treatment or placebo", with no more details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Llor 2012

Methods	Randomised double-blind, placebo-controlled trial
Participants	Participants: recruited from 13 primary care centres Inclusion criteria: aged > 40 years, diagnosis of mild to moderate COPD (smoking history > 10 pack-years, ratio of post-bronchodilator FEV_1:FVC of < 70%, post-bronchodilator FEV_1 > 50% of the predicted value), presence of an exacerbation (at least 1 of the following: increase of dyspnoea, increase in sputum volume, sputum purulence, or a combination) Exclusion criteria: antibiotic use in the previous 2 weeks, bronchial asthma, cystic fibrosis, bronchiectasis of origin other than COPD, active neoplasm, tracheotomy, need for hospital admission, immunosuppression, hypersensitivity to beta-lactams, clavulanate or lactose, institutionalisation, unable to provide informed consent Baseline demographics: 310 patients included; mean age 68 years, 81% male, mean FEV_1/FVC 62% Spirometrically confirmed COPD: yes Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 20 days Treatment group: amoxicillin/clavulanate 500/125 mg 3 times daily (oral) for 8 days Control group: placebo for 8 days
Outcomes	Primary outcome: clinical cure/improvement or failure at the end of therapy visit (days 9 to 11, physician assessed) Secondary outcome: clinical cure/improvement or failure at follow-up visit at day 20 Re-exacerbations (in 1 year - not analysed in this systematic review) Adverse events
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random-number table
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators and data assessors were masked to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, investigators and data assessors were masked to treatment allocation
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Manresa 1987

Methods	Randomised double-blind, placebo-controlled trial
Participants	Participants: patients admitted to hospital with exacerbation of COPD Inclusion criteria: at the time of a hospital admission: increase in symptoms (cough, dyspnoea, and volume and purulence of sputum) Exclusion criteria: evidence of parenchymal consolidation on chest X-ray or of other pulmonary or cardiac disease Baseline demographics: 19 patients included, mean age 67 years, % male, FEV_1 not stated Spirometrically confirmed COPD: no Severity of exacerbation: severe
Interventions	Mean follow-up: 13 days Treatment group: cefaclor 1.5 g/day (oral) for 8 days Control group: placebo for 8 days
Outcomes	Length of hospital stay
Notes	Research letter to the editor

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described ("double blind")
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described ("double blind")
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Nouira 2001

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Participants: patients admitted to medical ICU with exacerbation of COPD and need for mechanical ventilation Inclusion criteria: aged > 40 years; COPD diagnosed on the basis of clinical history, physical examination, and chest radiograph; acute respiratory failure requiring mechanical ventilation within the first 24 h of admission Exclusion criteria: antimicrobial treatment in the previous 10 days, alveolar infiltrates on

	chest X-rays, previously enrolled in the study. Known history of asthma or bronchiectasis, allergy to quinolone derivatives, pregnancy or breast feeding, terminally ill or immunocompromised, hepatic disease or severe renal impairment, gastrointestinal disease that could affect drug absorption, concomitant infection requiring systemic antibacterial therapy Baseline demographics: 93 patients included; mean age 66 years, 90% male, mean FEV_1 0.77 L/s Spirometrically confirmed COPD: no Severity of exacerbation: severe
Interventions	Mean follow-up: 10 days All patients were monitored until their discharge from hospital Treatment group: ofloxacin 400 mg/day (oral) for 10 days Control group: placebo for 10 days
Outcomes	Mortality Treatment failure (need for additional antibiotics and death combined) Length of hospital stay Adverse events
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to treatment or placebo using random numbers
Allocation concealment (selection bias)	Low risk	All drugs and placebo packages were prepared and numbered by the hospital pharmacy and were used consecutively. Assignments of patients were placed in closed envelopes with identification numbers that were stored in the ICU
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical appearance of the medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study investigators and hospital staff were masked to the treatment status until data completion
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Petersen 1967

Methods	Randomised, double-blind, controlled trial
Participants	Participants: patients admitted to hospital with exacerbation (not defined) of COPD Inclusion criteria: aged 45 to 75 years, chronic bronchitis (history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more successive years) Exclusion criteria: severe deformities of the spine or chest, localised or generalised specific lung disease, signs of cardiac insufficiency Baseline demographics: 19 patients included; mean age 62 years, 53% male Spirometrically confirmed COPD: no Severity of exacerbation: severe
Interventions	Mean follow-up: 10 days Treatment group: chloramphenicol 2 g/day for 10 day Control group: placebo for 10 day
Outcomes	Mortality Patient-reported well-being
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients: yes; personnel: no
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group got a clinical examination on day 0
Intention-to-treat-analysis	High risk	Drop-outs were not analysed (only per-protocol reported)

Pines 1968

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	Participants: patients admitted to hospital with exacerbation of symptoms of chronic bronchitis Inclusion criteria: > 50 years old, history of chronic bronchitis > 5 years and a history during the past 6 weeks of an exacerbation, male, moderately-to-severely illness on

Pines 1968 (*Continued*)

	admission (as judged by the receiving SHO), persistent purulent sputum and a PEFR < 200 L/min (unless too ill to do so) Exclusion criteria: allergy to penicillin, asthma, extensive bronchiectasis, active tuberculosis, lung cancer, sputum eosinophilia (> 10%) or blood urea > 60 mg/100 mL Baseline demographics: 30 patients, mean age 68 years, 100% males, FEV1 not reported Spirometrically confirmed COPD: No Severity of exacerbation: severe
Interventions	Mean follow-up: 14 days Treatment group: penicillin 6 million units/day for 14 days and streptomycin 1 g/day parenterally for 7 days Control group: placebo for 14 days
Outcomes	Treatment failure (physician reported) Mortality
Notes	Pilot trial of the paper

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Fisher and Yate's tables
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo injection", "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"blind assessors"
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Pines 1972

Methods	Randomised double-blinded controlled trial
Participants	Participants: patients admitted to hospital with exacerbation of COPD Inclusion criteria: aged > 60 years old, history of chronic bronchitis > 5 years and a definite history during the previous 6 weeks of an exacerbation, male, failure of at least 1 previous treatment with antibiotics, moderately severely ill on admission (as judged by the receiving SHO), persistent purulent sputum and PEFR < 200 L/min Exclusion criteria: asthma, bronchiectasis, other pulmonary disease or sputum eosinophilia (> 10%)

Pines 1972 (*Continued*)

	Baseline demographics: 259 patients included, mean age 71 years, 100% male, FEV_1 not reported Spirometrically confirmed COPD: no Severity of exacerbation: severe
Interventions	Mean follow-up: 12 days Exacerbations were followed at the beginning and end of trial and 1 and 4 weeks later Treatment groups 1 and 2: tetracycline hydrochloride 2 g/day or chloramphenicol 2 g/day orally for 12 days Control group: placebo for 12 days
Outcomes	Treatment failure (physician reported) day 12 Treatment failure (additional antibiotics) day 7 to 28 Mortality Adverse events
Notes	Patients with very severe exacerbation were not included for ethical reasons

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Fisher & Yate's tables
Allocation concealment (selection bias)	Low risk	The total course of capsules for each patient was put into a sealed bottle by an independent pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments were made by independent trained observers
Intention-to-treat-analysis	Low risk	No withdrawals

Sachs 1995

Methods	RCT
Participants	Participants: patients with general practitioner visit for new or aggravated respiratory (increase in dyspnoea with or without sputum production) symptoms Inclusion criteria: aged > 18 years, positive diagnosis of asthma or COPD made by a pulmonary physician during the previous 10 years Exclusion criteria: daily use of oral corticosteroids or antimicrobial drugs, diabetes mellitus, alcoholism, history of pulmonary surgery or tuberculosis, severe bronchiectasis, a

Sachs 1995 (*Continued*)

	psychiatric history Baseline demographics: 61 patients included; mean age ~ 52 years, % male and mean FEV_1 not stated Spirometrically confirmed COPD: unclear Severity of exacerbation: mild to moderate
Interventions	Mean follow-up: 35 days Treatment group: amoxicillin 1.5 g or co-trimoxazole 1.9 g/day orally for 7 days Control group: placebo for 7 days
Outcomes	Treatment success/failure (patient reported symptoms)
Notes	We included only the subgroup with COPD

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	List of random numbers
Allocation concealment (selection bias)	Low risk	Hospital pharmacist had the code of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ICU: intensive care unit; IV: intravenous; NYHA: New York Heart Association; PEFR: peak expiratory flow rate; RCT: randomised controlled trial; SD: standard deviation; SHO: senior house officer; TLC: total lung capacity; UTI: urinary tract infection.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aitchison 1968	No placebo group
Alix 1979	No placebo group
Allan 1966	No placebo group
Allegra 1996	No placebo group
Alvarez-Sala 2006	No placebo group
Andrijevic 2011	No comparison group
Anon 1969	No placebo group
Anon 1972	No placebo group
Banerjee 2001	No COPD exacerbations
Bekçi 2009	Participants did not have an exacerbation of COPD (stable patients)
Bennion-Pedley 1969	No placebo group
Braendli 1982	No placebo group
Burgi 1975	No placebo group
Burrow 1975	No placebo group
Chatterjee 2011	No placebo group
Chen 2000	No placebo group
Christiansen 1963	No placebo group
Citron 1969	Not an RCT
Dong 2005	No placebo group
Douglas 1957	Not randomised and study had no placebo group
Egede 1993	No placebo group
Elmes 1965	Not randomised. Matched pairs
Fartoukh 2004	Protocol. Trial stopped due to recruitment problems

(*Continued*)

Filipovic 2000	No placebo group
Francis 1960	Use of long-term prophylactic antibiotics
Francis 1964	No placebo group
Fruensgaard 1972	No placebo group
Gaillat 2007	No placebo group
Gocke 1964	No placebo group
Goddard 2003	Not an RCT
Gomez 2000	Prophylactic antibiotic use. Patients treated with azithromycin 500 mg/day for 3 days every 21 days during the winter months, and a control group without treatment
Gotfried 2007	No placebo group
Guerin 1987	No placebo group
Haanaes 1980	No placebo group
Hansen 1986	Not an RCT
Hansen 1990	No clinical outcomes
Hauke 2002	No placebo group
Hopkins 1962	No placebo group
Jacobsen 2002	Not an RCT but a retrospective chart review
Jia 2010	No placebo group
Johnston 1961	Study assessed outcomes of long-term antibiotic use in stable patients (no exacerbation)
Kaul 1967	No placebo group
King 1996	Study not in patients with COPD but in patients with acute bronchitis
Leophonte 1998	Study not in patients with COPD but in patients with acute bronchitis
Lirsac 2000	No placebo group. In addition the antibiotic treatment group also received fenspiride (from day 0 to day 30) and the control group received a placebo
Maesen 1976	No placebo group

(*Continued*)

Maesen 1980	No placebo group
Malone 1968	No placebo group
May 1964	No placebo group
Miravitlles 2009	Study compared participants with stable disease (no exacerbation)
NCT00255983	This study terminated early (financial reasons)
Nicotra 1982	No clinical outcomes
Nonikov 2001	No placebo group
Parnham 2005	Study looked at participants with stable disease (no exacerbation)
Peng 2003	Not an RCT but a retrospective cohort study
Pham 1964	Not an RCT
Pines 1967	No placebo group
Pines 1969	No placebo group
Pines 1972a	No placebo group
Pines 1973	No placebo group
Pines 1973a	No placebo group
Pines 1974	Not an RCT
PRITZL 1959	Not an RCT
Puchelle 1975	No placebo group
Pugh 1964	No placebo group
Rethly 1961	Not an RCT
Roede 2007	Placebo group began after 3 days of antibiotics in both groups
Romanovskikh 2007	No placebo group
Ross 1973	No placebo group
Sethi 2007	No placebo group

(*Continued*)

Sethi 2010	Study looked at participants with stable disease (no exacerbation)
Smyllie 1972	No placebo group
Sohy 2002	Not an RCT but a narrative review
Soler 2003	No placebo group
Stolz 2007	No placebo group
Suzuki 2001	Prophylactic antibiotic use
Tremolieres 2000	No placebo group
Williams 1981	No placebo group
Wilson 2004	No placebo group in trial. Moxifloxacin was compared to standard antibiotic therapy
Wilson 2011	No placebo group
Wilson 2012	Head-to-head trial of 2 different antibiotics regimens
Zapulla 1988	No placebo group
Zervos 2005	No placebo group

COPD: chronic obstructive pulmonary disease; RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01091493

Trial name or title	Utility of Antibiotic Treatment in Non-purulent Exacerbations of Chronic Obstructive Pulmonary Disease: a Double Blinded, Randomized, Placebo-controlled Trial of Security and Efficacy (AEPOC-ATB)
Methods	RCT
Participants	Inclusion criteria: aged 40 to 90 years; COPD diagnosis according to GOLD guidelines; hospitalisation for any acute exacerbation of COPD; failure of outpatient treatment, increasing dyspnoea in the previous days; co-morbidity that caused detriment of respiratory function Exclusion criteria: life expectancy of < 6 months; mechanical ventilation; cardiovascular condition that causes exacerbation; immunosuppression; pulmonary infiltrates that suggest pneumonia; antibiotic treatment in the last month; pregnancy; ECG with a large QT segment; hypokalaemia; hepatic failure or renal failure

NCT01091493 (*Continued*)

Interventions	Drug: moxifloxacin 400 mg administered once a day for 5 days Control: no intervention
Outcomes	Primary outcome measures: efficacy of treatment WITHOUT antibiotics in non-purulent exacerbations of COPD (time frame: 6 months) Secondary outcome measures: efficacy/safety in treatment on re-hospitalisations at 6 months (time frame: 6 months); in-hospital stay (days) (time frame: 6 months); all-cause mortality (time frame: 1 and 6 months) ; determination of procalcitonin (time frame: hospitalisation day 1, 1 month and 6 months); quality of life measured by the St George's Respiratory Questionnaire (time frame: hospitalisation day 1 and 6 months); measure of CRP (time frame: hospitalisation day 1, 1 month and 6 months); measure of cytokines (IL-1, IL-6, IL-8, IL-10) (time frame: hospitalisation day 1, 1 month and 6 months); measure of TNF-α (time frame: hospitalisation day 1, 1 month and 6 months)
Starting date	July 2010
Contact information	Nestor Soler, M.D., Ph.D. email:nsoler@clinic.ub.es
Notes	-

COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECG: electrocardiogram; IL: interleukin; RCT: randomised controlled trial; TNF-α: tumour necrosis factor-alpha.

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo

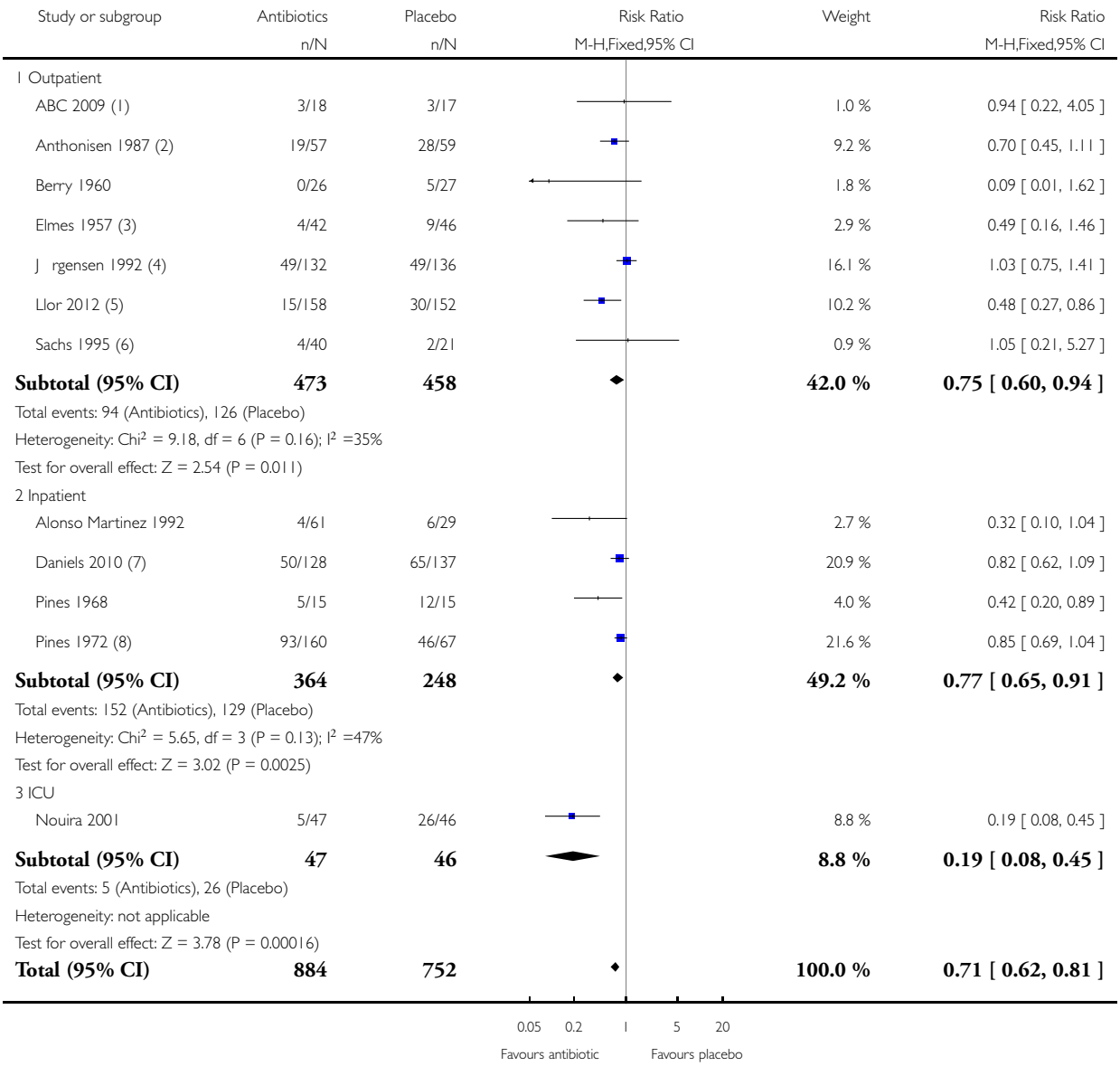
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics)	12	1636	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.62, 0.81]
1.1 Outpatient	7	931	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.94]
1.2 Inpatient	4	612	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.65, 0.91]
1.3 ICU	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.08, 0.45]
2 Treatment failure within 4 weeks - current drugs only	8	1175	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.64, 0.91]
2.1 Outpatient	5	790	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.63, 1.01]
2.2 Inpatient	3	385	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.55, 0.92]
3 Adverse events	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Diarrhoea	3	698	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.62 [1.11, 6.17]
3.2 Dyspepsia	2	605	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.28, 1.73]
3.3 Pain in mouth	1	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.73 [0.80, 74.98]
3.4 Exanthema, itching	3	698	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.83 [0.77, 19.11]
3.5 Overall (adverse events not separated)	5	1243	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [1.03, 2.27]
4 All-cause mortality	5	624	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.25, 1.16]
4.1 Inpatients	4	531	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.37, 2.79]
4.2 ICU patients	1	93	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.06, 0.72]
5 Duration of hospital stay (days)	3	202	Mean Difference (IV, Random, 95% CI)	-3.04 [-8.83, 2.76]
6 Improvement in dyspnoea measured at the end of the study period	2	300	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.96, 0.15]
6.1 Outpatients	1	35	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.97, 0.97]
6.2 Inpatients	1	265	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.27, 0.07]
7 Health-related quality of life or functional status measures	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Days off work	1	88	Mean Difference (IV, Fixed, 95% CI)	-5.18 [-6.08, -4.28]

Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics).

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

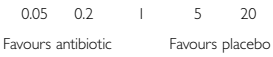
Outcome: 1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics)



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 251 (Antibiotics), 281 (Placebo)					
Heterogeneity: Chi^2 = 26.34, df = 11 (P = 0.01); I^2 =58%					
Test for overall effect: Z = 4.95 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 9.85, df = 2 (P = 0.01), I^2 =80%					



(1) 28 days,

(2) within 21 days

(3) time point unclear;reported for exacerbations only.under the assumption that it happened to every pat once we took patients instead

(4) day 8

(5) 20 days

(6) failure between 4-24 days

(7) day 30

(8) additional antibiotics (day 7-28)

Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Treatment failure within 4 weeks - current drugs only.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Treatment failure within 4 weeks - current drugs only

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Outpatient					
ABC 2009 (1)	3/18	3/17		1.6 %	0.94 [0.22, 4.05]
Anthonisen 1987 (2)	19/57	28/59		14.1 %	0.70 [0.45, 1.11]
J rgensen 1992 (3)	49/132	49/136		24.8 %	1.03 [0.75, 1.41]
Llor 2012 (4)	15/158	30/152		15.7 %	0.48 [0.27, 0.86]
Sachs 1995 (5)	4/40	2/21		1.3 %	1.05 [0.21, 5.27]
Subtotal (95% CI)	**405**	**385**		**57.5 %**	**0.80 [0.63, 1.01]**
Total events: 90 (Antibiotics), 112 (Placebo)					
Heterogeneity: Chi² = 5.93, df = 4 (P = 0.20); I² =33%					
Test for overall effect: Z = 1.91 (P = 0.056)					
2 Inpatient					
Alonso Martinez 1992	4/61	6/29		4.2 %	0.32 [0.10, 1.04]
Daniels 2010 (6)	50/128	65/137		32.2 %	0.82 [0.62, 1.09]
Pines 1968	5/15	12/15		6.2 %	0.42 [0.20, 0.89]
Subtotal (95% CI)	**204**	**181**		**42.5 %**	**0.71 [0.55, 0.92]**
Total events: 59 (Antibiotics), 83 (Placebo)					
Heterogeneity: Chi² = 4.74, df = 2 (P = 0.09); I² =58%					
Test for overall effect: Z = 2.59 (P = 0.0095)					
Total (95% CI)	**609**	**566**		**100.0 %**	**0.76 [0.64, 0.91]**
Total events: 149 (Antibiotics), 195 (Placebo)					
Heterogeneity: Chi² = 11.13, df = 7 (P = 0.13); I² =37%					
Test for overall effect: Z = 3.10 (P = 0.0020)					
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² =0.0%					

(1) 28 days,

(2) within 21 days

(3) day 8

(4) 20 days

(5) failure between 4-24 days

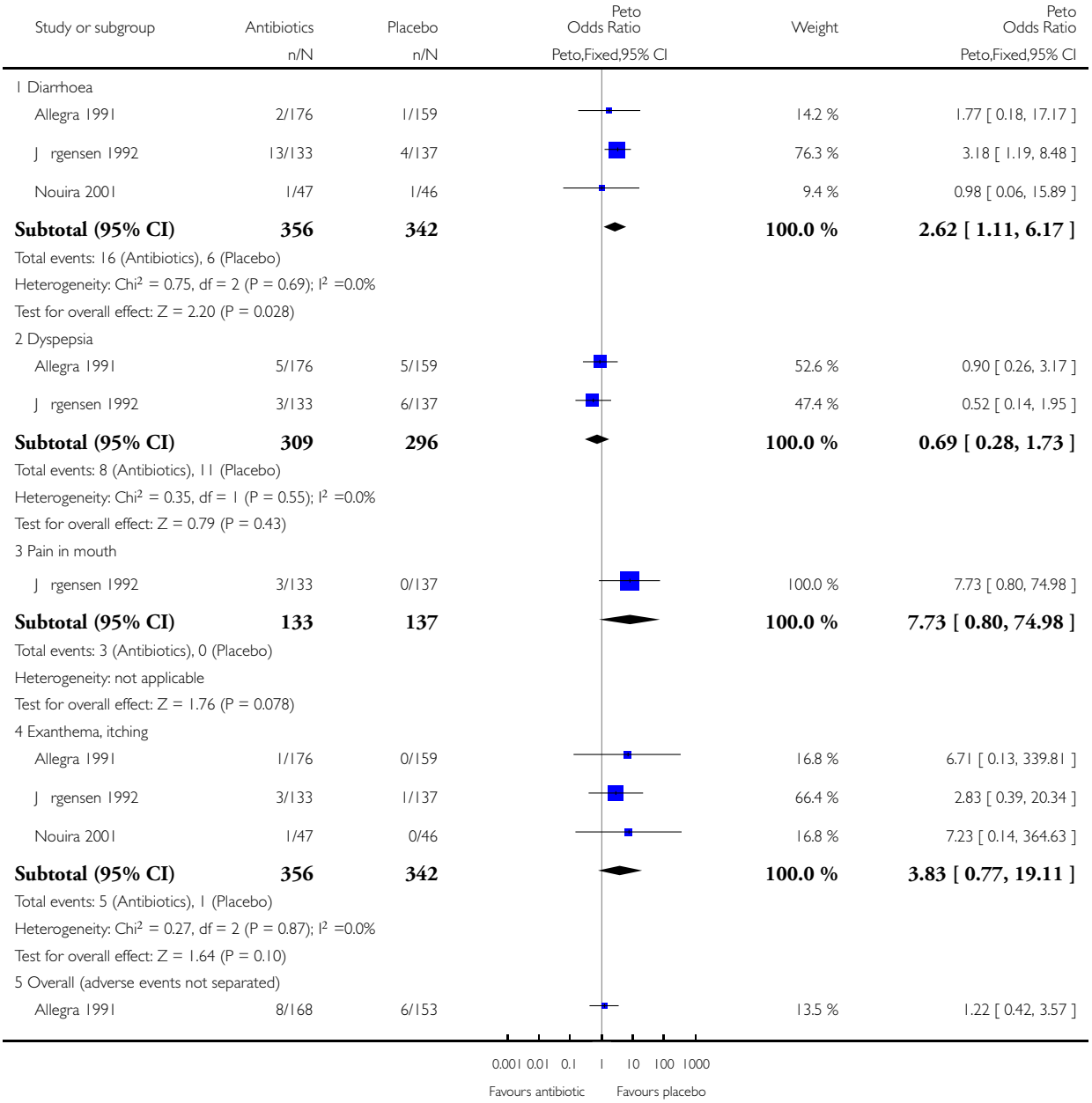
(6) day 30

Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Adverse events.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 3 Adverse events



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Antibiotics n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Daniels 2010	4/133	5/125		8.8 %	0.75 [0.20, 2.81]
J rgensen 1992	27/133	18/137		38.0 %	1.67 [0.88, 3.17]
Llor 2012	23/158	12/152		31.4 %	1.94 [0.96, 3.92]
Nouira 2001	5/42	4/42		8.2 %	1.28 [0.32, 5.06]
Subtotal (95% CI)	**634**	**609**		**100.0 %**	**1.53 [1.03, 2.27]**
Total events: 67 (Antibiotics), 45 (Placebo)					
Heterogeneity: Chi^2 = 1.87, df = 4 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 2.12 (P = 0.034)					

Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 All-cause mortality.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

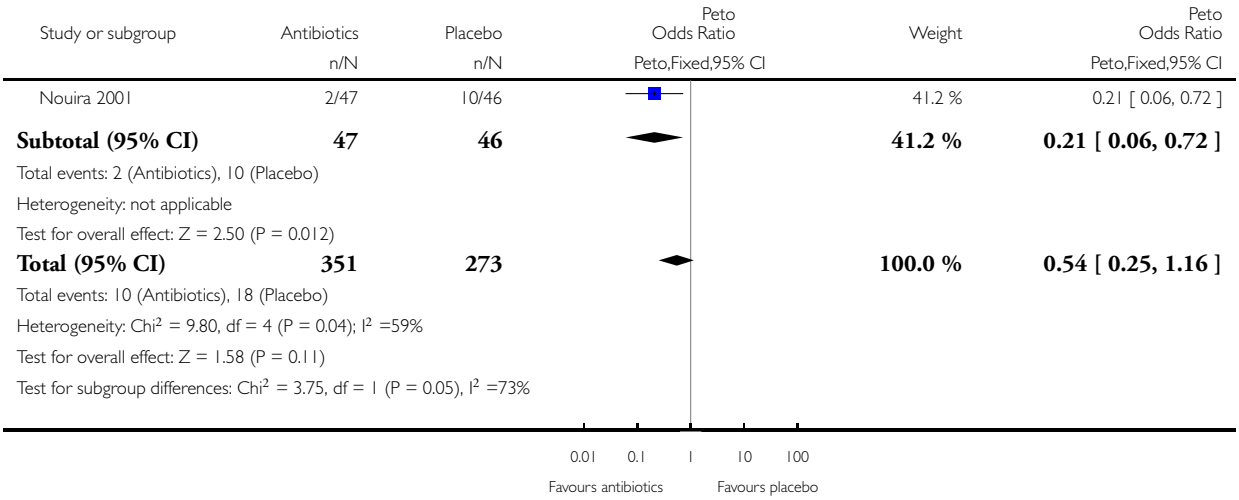
Comparison: 1 Antibiotics versus placebo

Outcome: 4 All-cause mortality

Study or subgroup	Antibiotics n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Inpatients					
Pines 1972	0/173	1/86		3.5 %	0.05 [0.00, 3.16]
Petersen 1967	0/9	1/10		3.9 %	0.15 [0.00, 7.58]
Pines 1968	1/15	3/15		14.0 %	0.33 [0.04, 2.60]
Daniels 2010	7/107	3/116		37.4 %	2.51 [0.71, 8.90]
Subtotal (95% CI)	**304**	**227**		**58.8 %**	**1.02 [0.37, 2.79]**
Total events: 8 (Antibiotics), 8 (Placebo)					
Heterogeneity: Chi^2 = 6.05, df = 3 (P = 0.11); I^2 =50%					
Test for overall effect: Z = 0.03 (P = 0.98)					
2 ICU patients					

(*Continued* . . .)

(. . . *Continued*)

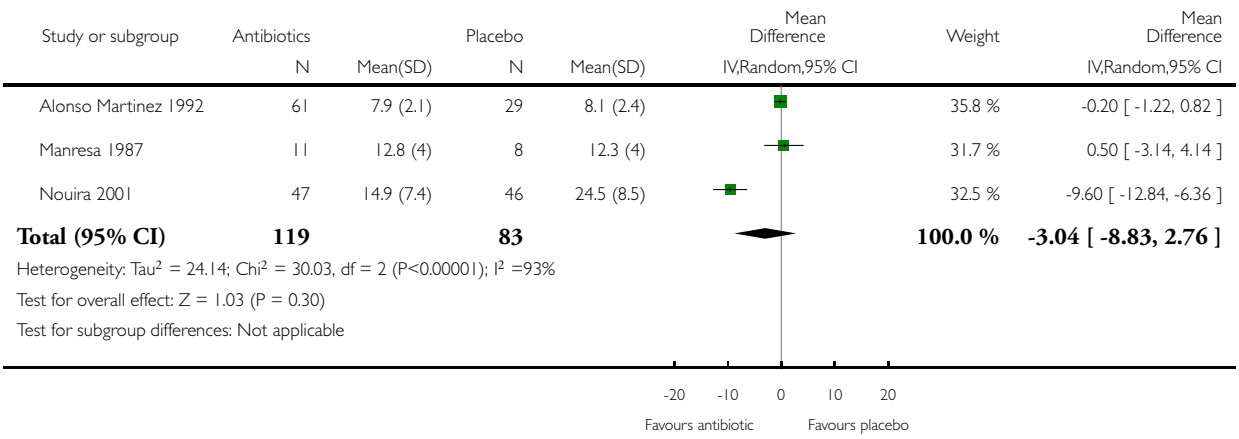


Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 Duration of hospital stay (days).

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 5 Duration of hospital stay (days)



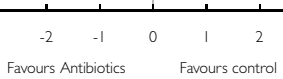
Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 Improvement in dyspnoea measured at the end of the study period.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 6 Improvement in dyspnoea measured at the end of the study period

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Outpatients							
ABC 2009	18	0.5 (1.3)	17	0.5 (1.6)		32.6 %	0.0 [-0.97, 0.97]
Subtotal (95% CI)	**18**		**17**			**32.6 %**	**0.0 [-0.97, 0.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 Inpatients							
Daniels 2010	128	-2.4 (2.8)	137	-1.8 (2.8)		67.4 %	-0.60 [-1.27, 0.07]
Subtotal (95% CI)	**128**		**137**			**67.4 %**	**-0.60 [-1.27, 0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.74 (P = 0.081)							
Total (95% CI)	**146**		**154**			**100.0 %**	**-0.40 [-0.96, 0.15]**
Heterogeneity: Chi^2 = 0.99, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 1.43 (P = 0.15)							
Test for subgroup differences: Chi^2 = 0.99, df = 1 (P = 0.32), I^2 =0.0%							



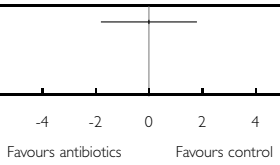
Analysis 1.7. Comparison 1 Antibiotics versus placebo, Outcome 7 Health-related quality of life or functional status measures.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 7 Health-related quality of life or functional status measures

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
ABC 2009 (1)	18	-2.3 (2.7)	17	-2.3 (2.7)		0.0 [-1.79, 1.79]



(1) CCQ

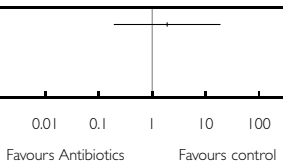
Analysis 1.8. Comparison 1 Antibiotics versus placebo, Outcome 8 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates).

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 8 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ABC 2009 (1)	2/18	1/17		1.89 [0.19, 18.97]



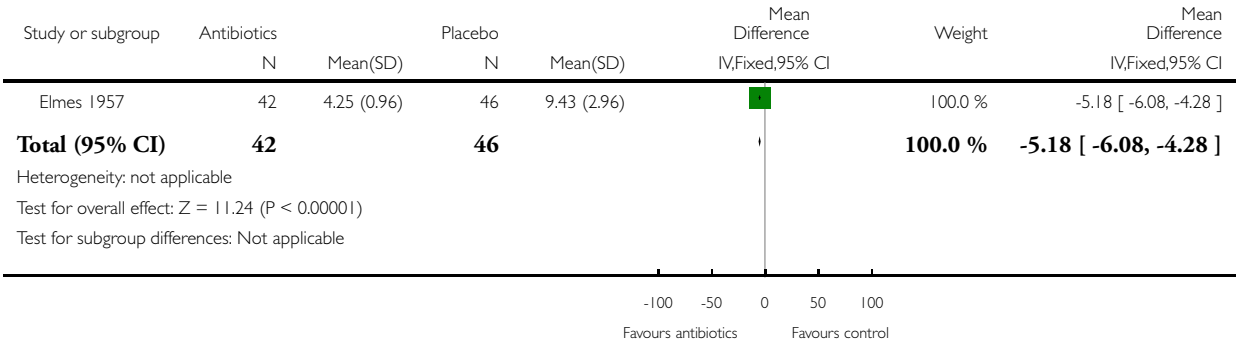
(1) relapse within 4 weeks

Analysis 1.9. Comparison 1 Antibiotics versus placebo, Outcome 9 Days off work.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 9 Days off work



ADDITIONAL TABLES

Table 1. Type and dose of antibiotic used

Study	Antibiotic	Dose	Duration	Currently available and used?	Co-interventions	Control
ABC 2009	Amoxicillin-clavulanic acid (oral)	1.5 g/day	7 days	Yes	Oral prednisolone 30 mg for 7 days	Placebo for 7 days and oral prednisolone 30 mg for 7 days
Allegra 1991	Amoxicillin-clavulanic acid (oral)	2 g/day	5 days	Yes		Placebo
Alonso Martinez 1992	Trimethoprim-sulphamethoxazole or amoxicillin/clavulanic acid	1.9 g/day	8 days	Yes		
Anthonisen 1987	Trimethoprim/sulphamethoxazole (oral)	1.9 g/day	10 days	Yes		Placebo

Table 1. Type and dose of antibiotic used (*Continued*)

	Amoxicillin (oral)	1 g/day				
	Doxycycline (oral)	0.1 to 0.2/day				
Berry 1960	Oxytetracycline (oral)	1 g/day	5 days	No		Placebo
Daniels 2010	Doxycycline (oral)		7 days	Yes	IV prednisolone taper	Placebo plus IV prednisolone taper
Elmes 1957	Oxytetracycline (oral)	1 g/day	5 to 7 days	No		Placebo
Fear 1962	Oxytetracycline (oral)	1 g/day	7 days	No		placebo
Jørgensen 1992	Amoxicillin (oral)	1.5 g/day	7 days	Yes		placebo
Llor 2012	Amoxicillin/ clavulanate (oral)	1.5 g/day	8 days	Yes		Placebo
Manresa 1987	Cefaclor (oral)	1.5 g/day	8 days	Yes		placebo
Nouira 2001	Ofloxacin (oral)	400 mg/day	10 days	Yes		placebo
Petersen 1967	Chloramphenicol (oral)	2 g/day	10 days	No		placebo
Pines 1968	Penicillin (parenterally)	1 g/day	14 days	Yes		placebo
Pines 1972	Tetracycline hydrochloride (oral) or Chloramphenicol	2 g/day	12 days	No		placebo
Sachs 1995	Amoxicillin 1.5 g/day 1.9 g/day (oral)	1.5 g/day	7 days	yes		placebo
	or co-trimoxazole	1.9 g/day				

IV: intravenous.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*T he Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

CONTRIBUTIONS OF AUTHORS

All authors conceived the idea for the review and wrote the protocol.

DV, HJ and CSS contributed towards the following: trial selection, data and trial characteristics extraction.

MAP, JGA, DV checked the data extraction.

DV and MAP contributed to trial grading.

DV wrote the first draft and all authors critically reviewed the draft.

DV and MP are the guarantors for this review.

DECLARATIONS OF INTEREST

Claudia Steurer-Stey has lectured for the antibiotic-producing companies AstraZeneca, GlaxoWellcome, Merck Sharp & Dome, Pfizer and Novartis. The remaining four authors (DV, HJ, JGA and MAP) do not have any known conflicts of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had to change our primary outcome from treatment failure within two weeks to four weeks because the reporting of the time of the end point was too heterogeneous.

Some outcomes were not reported at all (hospital admission, admission to an ICU).

We did not analyse subgroups on duration of antibiotic intervention or type of antibiotic intervention because the number of studies was too small.

INDEX TERMS

Medical Subject Headings (MeSH)

Ambulatory Care; Anti-Bacterial Agents [adverse effects; *therapeutic use]; Disease Progression; Hospitalization; Intensive Care Units; Pulmonary Disease, Chronic Obstructive [classification; *drug therapy; mortality]; Randomized Controlled Trials as Topic; Treatment Failure

MeSH check words

Humans